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Developing Treatment, Treatment Validation, and Treatment Scope in the Setting of an Autism Clinical Trial

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14. ABSTRACT

We submitted and received approval for our latest Continuing Review (CR). In addition an amendment was submitted and approved to use AutismMatch to help increase the rate of subject recruitment. We applied for and received an additional 6 month no cost extension to maximize our ability to collect subjects. Task #2 has been completed. We had a significant set back in the beginning of the year for Task #3. Our LC-MSMS suffered a catastrophic failure early in November 2011 and repairs were not finished until January 4, 2012. Upon repair and calibration we resumed optimizing analysis conditions including conditions for three additional isoprostanes. We began Task #4, sample analysis. We completed initial analysis of the first 18 pre and 18 post treatment samples.We will complete Task #4 and once all subjects have finished treatment. Tasks # 5 and 6 will be completed once subject treatment has finished. Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0730

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Introduction:

This project is to test to see if DHA treatment can beneficially affect excretion of urinary biomarkers of oxidative stress and the autism clinical phenotype. In addition polymorphic variants of genes of certain enzymes that synthesize and metabolize docosahexaenoic acid (DHA) may contribute to the phenotype of some autism cases. We will test to see if any of these genes are risk factors for autism. We will also measure changes in excretion of the polyunsaturated fatty acid (PUFA) derived biomarkers of oxidative stress (isoprostanes and neuroprostanes) together with the changes in production of anti-inflammatory lipid mediators. We will test these biomarkers to see if we can monitor and validate effectiveness of DHA therapy. We will also test the genotypes of key DHA-metabolizing enzymes can predict which patients will respond to therapy Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0730.

Body:

PROJECT #2: PI T.P. STEIN, PhD, PARTNERING PI, W81XWH-08-1-0729

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0730.

Unless otherwise stated, tasks are divided between the synthetic core (directed by Dr. B.W. Spur) and the Analytical core (directed by Dr. T.P. Stein).

Task #1 Obtain IRB approval (Drs. Stein and Spur).

Our latest Continuing Review was approved on September 27th 2012. An amendment was submitted along with this continuing review to remove Rakhee Wasiulla from the study who has left the university. Also in the amendment was an extension of the end date of the study. These changes were also approved by our (Institutional Review Board) IRB on September 27th 2012. The approved CR was sent to the HRPO on October 4th 2012. Please also see partnering project W81XWH-08-1-0728 Tasks #1 and #2.

Additional amendments in the past year:
We submitted an amendment on January 18th 2012 to allow us to recruit from AutismMatch. Included in this amendment were a new consent, a new flier and an updated protocol. This amendment was approval on February 29th 2012.

Task #2 **After IRB approval has been obtained and permission given to proceed we (B.W. Spur and A. Rodriguez) will chemically synthesize the protective lipid metabolites: (i) Lipoxin A4 (LXA4, 5S, 6R,15S-trihydroxyl-7, 9,13-trans-11-cis-eicosatetraenoic acid), (ii) lipoxin A4 precursor, 15-hydroxy-eicosatetraenoic acid, (iii) Resolvin D1 (RvD1, 7S,8R,17S trihydroxy-4Z,9E,11E,13Z,15E, 19Z-**

docosahexaenoic acid) (iv) Resolvin D precursor (17-hydroxy-docosahexaenoic acid), (v) Resolvin E1 (RvE1, 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16 Eicosapentaenoic acid and (vi) Protectin D1 (10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E, 15Z,19Z-hexaenoic acid) all with and without a deuterium label. It is expected that task #2 will take two years ((21-42 months) as stated in the current SOW).

This task was completed in the previous year.

Task #3 **(i) Year 1 and the first half of year two were spent in developing isotope dilution LC-MSMS assays for the compounds referenced in task #2 (T.P. Stein and technician). Also done during that year are to replicate in our laboratory published LC-MSMS assays for isoprostane and isoprostane metabolites in urine, 2,3 dinor-5,6 dihydro-PGF2t and iPF4α-VI (T.P. Stein and technician).**

We continued optimizing analysis conditions. Additional progress was limited in the first quarter due to a breakdown of our LC-MSMS. The LC-MSMS suffered a catastrophic failure early in November and repairs were not finished within the time frame of this report (repairs completed on January 4, 2012). The two major problems were failure to identify masses correctly and system instability. The instrument was under a full service contract with Agilent Technologies. After each 'fix' the instrument would work for a day or two and then the problem would return, A service representative spent more than 10 days in our facility and ultimately had to replace nearly all of the electronics. We thoroughly tested the system and it is now in proper working order. The methods used here are state of the art and labor intensive. We therefore continued optimizing analysis conditions and have added three additional isoprostanes, 8-iso-15(R) PGF2α, 11-b-PGF2α and 15(R)-PGF2α (2).

Task #4 **Use the newly developed assays from task #3 to measuring the markers (isoprostane and it's metabolite, LXA4, RvD1, RvE1 and Protectin), in the urines collected as part of the clinical trial. We anticipate 66 (placebo-treated) and 66 (DHA-treated) subjects; initially two urines pre-treatment and two at the end of the treatment phase will be analyzed for each metabolite. This task will be started one year after the start of patient sample collection. We anticipate having to do multiple LC-MSMS injections because while sample preparation will be common, LC conditions for resolution may well be different (T.P. Stein and technician).**

Table 1

(a) ALL DATA	PRE		POST	
	MEAN ± SEM, ng/ml	N	MEAN ± SEM, ng/ml	N
8-iso-PGF2α	0.33 ± 0.06	18	0.36 ± 0.03	18
8-iso-15(R) PGF2α	0.34 ± 0.10	17	0.39 ± 0.05	18
11-b-PGF2α	0.06 ± 0.02	12	0.17 ± 0.05	13
15(R)-PGF2α	0.30 ± 0.22	18	0.22 ± 0.02	18
PGF2α	0.59 ± 0.14	18	0.81 ± 0.12	18
(b) MINUS TWO OUTLIERS				
8-iso-PGF2α	0.26 ± 0.03	16	0.34 ± 0.03	16
8-iso-15(R) PGF2α	0.23 ± 0.04	16	0.36 ± 0.05	16
11-b-PGF2α	0.06 ± 0.02	12	0.16 ± 0.05	12
15(R)-PGF2α	0.26 ± 0.08	16	0.22 ± 0.02	16
PGF2α	0.47 ± 0.11	16	0.75 ± 0.12	16
(c) TWO OUTLIERS				
8-iso-PGF2α	0.94 ± 0.34	2	0.38 ± 0.03	2
8-iso-15(R) PGF2α	1.23 ± 0.05	2	0.52 ±0.08	2
11-b-PGF2α	ND	2	ND	2
15(R)-PGF2α	0.63 ± 0.34	2	0.34 ± 0.03	2
PGF2α	1.58 ± 0.57	2	1.29 ± 0.57	2

Table 1. Summary of complete (pre treatment and post – 12 weeks of either placebo or DHA treatment) data for Isoprostane isomers. The parent molecule for isoprostanes (PGF2α) is included as a reference marker. (a). All of the data combined; (b) Data set with the two outliers removed and (c) data for the two outliers.

We have so far analyzed 18 sets of urines (pre-post treatment). We began analysis in the third quarter as soon as we were confident that our LC-MSMS was fixed and re-calibrated and working properly. These samples have been analyzed for isoprostanes; other analyses are in progress. The quality of the data is excellent; two of the subjects showed consistently very high isoprostane levels. The majority of work, including our earlier work which showed increased isoprostane levels in a subset of children with ASD measured 8-iso-PGF2α. More recently analytical methods have improved and it has proven to be possible to measure other urinary isoprostanes and we are doing so. The reason for adding other isoprostanes that finding the same result across a family of

compounds provides confirmatory support for measurements made on a single isoprostane.

For a number of reasons, including a desire to make a realistic assessment of whether running additional subjects we would need to address to our goals we asked the appropriate authorities to partially break the code for these 18 subjects. (Partial code breaking was restricted to treatment or non-treatment, no clinical information).

Table 1 should be interpreted in the context of this information. The four isoprostanes tracked each other closely. There was considerable scatter in the data; most of the scatter could be attributed to two outliers (tables 1b and 1c). There were two outliers. Removing these two outliers (table 1b) greatly reduced the variance for the other sample (table 1c). Analyzing the data in tables 1a and 1b by treatment group shows that even with a very large n, no effect of DHA treatment on isoprostane excretion is to be expected.

The story is very different for the two outlier with the very high isoprostane levels. First our previously published data showed that there was a subset of ASD children with elevated 8-iso-PGF2α levels, so this finding is both expected and confirmatory. Secondly, unlike the rest of the cohort, 1c shows that there was a large (>50%) reduction is oxidative stress after 12 weeks of DHA treatment. Inferences are: (i), this preliminary data is fully consistent with the biochemical aspects of our hypothesis that DHA treatment will reduced oxidative stress in oxidatively stressed ASD patients, (ii) the number of subjects needed to obtain significance is going to be in the 4-6 range and this is very feasible for us.

Of course the ultimate questions of interest are, who are the minority with high isoprostane levels, Is there any relationship to clinical status or genotype? This will be determined when the code is broken.

We continue to analyze samples until all subjects have completed the trial.

Task 5
Data will be collected and analyzed (04 year as per the current SOW, S Buyske).

Beyond the partial de-coding for the purposes of assessing progress, this task will not begin until subject recruitment, enrollment, treatment and analysis have been completed.

Task 6
Manuscripts prepared and submitted for publication (04 year as per the current SOW, all investigators)

This task will not begin until subject data analysis has been completed.

Key Research Accomplishments

We now have enough data to predict with reasonable certainty that we will be able to provide a definitive answer to the question: Does DHA supplementation reduce oxidative stress in ASD children with high levels of oxidative stress.

Reportable Outcomes:

Grant submission:

- We submitted a grant with Dr. Stein as the PI and with Drs. Ming and Johnson as Co-PIs to NIH entitled: Glucuronidation and Autism. The proposal was not awarded but the reviewers comments were encouraging and helpful and the grant was resubmitted this September.

Presentation:

- A poster presentation at the Autism NJ Jersey State Autism conference titled "Polyunsaturated fatty acid metabolism in Autism" was well received.

Papers and abstracts published/submitted:

- Rodriguez A.R., Spur B. W. Total synthesis of the macrophage derived anti-inflammatory lipid mediator Maresin 1. Tetrahedron Lett. 53, 4169-4172, 2012.
- Rodriguez A.R., Spur B. W. Total synthesis of the anti-inflammatory lipid mediator Resolvin E2. Tetrahedron Lett. 53, 1912-1915, 2012.
- Rodriguez A.R., Spur B. W. First total synthesis of the anti-inflammatory lipid mediator Resolvin D6. Tetrahedron Lett. 53, 85-89, 2012.
- An abstract was submitted to the 4th International conference on Lipid mediators. T.P. Stein PhD, X. Ming MD, PhD, M.D. Schluter BS, A. Rodriguez PhD, B.W. Spur PhD and G. Lambert MD. POLYUNSATURATED FATTY ACIDS METABOLISM IN AUTISM:
- Rodriguez A.R.,Spur B. W.Total synthesis of Resolvin D1, a potent anti-inflammatory lipid mediator. Tetrahedron Lett. submitted 2012.

Conclusion:

In summary, we are now collecting high quality data, a preliminary inspection of the results to date confirm our previously published findings that there is a subset of children with ASD who have high levels of oxidative stress and the data suggest that the oxidative stress is attenuated by DHA supplementation. It remains to collect more data on other metabolites, (in progress) on this sub-group and then, once the code is broken determine whether there were any clinical or genotypic correlations.

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Appendix:

Please find attached:

- Rodriguez A.R., Spur B. W. Total synthesis of the macrophage derived anti-inflammatory lipid mediator Maresin 1. Tetrahedron Lett. 53, 4169-4172, 2012.
- Rodriguez A.R., Spur B. W. Total synthesis of the anti-inflammatory lipid mediator Resolvin E2. Tetrahedron Lett. 53, 1912-1915, 2012.
- Rodriguez A.R., Spur B. W. First total synthesis of the anti-inflammatory lipid mediator Resolvin D6. Tetrahedron Lett. 53, 85-89, 2012.
- Rodriguez A.R.,Spur B. W.Total synthesis of Resolvin D1, a potent anti-inflammatory lipid mediator. Tetrahedron Lett. submitted 2012..

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Total synthesis of the macrophage derived anti-inflammatory lipid mediator Maresin 1

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ABSTRACT

The total synthesis of Maresin 1, an endogenous macrophage pro-resolving lipid mediator derived from docosahexaenoic acid, has been achieved. The chiral hydroxy-group at C7 was obtained via a Jacobsen hydrolytic kinetic resolution of a terminal epoxide whereas the center at C14 arises from a chiral pool strategy starting from 2-deoxy-D-ribose. Pd^0/Cu^I Sonogashira coupling of the two key fragments and Zn(Cu/Ag) reduction completed the total synthesis of Maresin 1.

The role of inflammation in diseases such as atherosclerosis, asthma, Alzheimer's disease, and cancer is well documented.[1–3] Interventions with eicosapentaenoic and docosahexaenoic acids (fish oil) were investigated to explore their effects on neutrophil function and leukotriene generation, and clinical improvements have been reported.[4–6] Serhan et al. investigated the molecular mechanism that controls acute inflammation and its resolution. They could show that during the resolution phase of inflammation enzymatic metabolism of these polyunsaturated fatty acids produced a series of powerful anti-inflammatory lipid mediators, the Resolvins, and Neuroprotectin D1.[7] Recently they discovered a novel macrophage derived mediator of inflammation resolution named Maresin 1 (Macrophage mediator in resolving inflammation).[8] Later on the complete stereochemical structure of Maresin 1 was established as (4*Z*,7*R*,8*E*,10*E*,12*Z*,14*S*,16*Z*,19*Z*)-7,14-dihydroxy-4,8,10,12,16,19-docosahexaenoic acid.[9] This product is formed in vivo from docosahexaenoic acid via *S*-selective 14-lipoxygenation to produce the hydroperoxide intermediate that undergoes epoxide formation followed by enzymatic hydrolysis to produce Maresin 1 (Fig. 1). Maresin 1 is a potent mediator that inhibits PMN infiltration, stimulates macrophage phagocytosis of apoptotic cells and controls pain similar to Resolvin E1.[8,9]

The growing interest to study the pharmacological properties of the Resolvins, Neuroprotectin D1, and Maresin 1 combined with the limited availability from natural sources requires their preparation by total syntheses.[10–23]

The first total synthesis of Maresin 1 was reported by Inoue co-workers.[16] The key features of Inoue's strategy encompass the BF_3-mediated alkyne attack on an epoxide, chiral titanium complex promoted enantioselective alkyne addition to an aldehyde, and a modified Julia–Kocienski olefination.

In this Letter, we wish to report a different synthetic strategy toward the total synthesis of Maresin 1 [MaR1; (4*Z*,7*R*,8*E*,10*E*,12*Z*,14*S*,16*Z*,19*Z*)-7,14-dihydroxy-4,8,10,12,16,19-docosahexaenoic acid; (**1**)]. As shown in the retrosynthetic approach to Maresin 1 (Fig. 2), the chiral center at C7 was obtained via a Jacobsen hydrolytic kinetic resolution of a terminal epoxide whereas 2-deoxy-D-ribose was used as the source of chirality for C17. Pd^0-Cu^I catalyzed Sonogashira coupling followed by Zn(Cu/Ag) reduction provided Maresin 1 (**1**).

The synthesis of the C1–C11 chiral fragment **2** was achieved as outlined in Scheme 1. CuI catalyzed coupling of allyl bromide (**6**) with 4-pentyn-1-ol (**7**) in H_2O according to the method of Bieber and Da Silva.[24] gave cleanly 7-octen-4-yn-1-ol (**8**) that was purified by vacuum distillation (bp 90–100 °C/7 mmHg). Jones oxidation of **8** followed by esterification with CH_3OH/2,2-dimethoxypropane in the presence of a catalytic amount of TMSCl at room temperature gave **9** (90%).[25] Epoxidation with 3-chloroperoxybenzoic acid in CH_2Cl_2 in the presence of $NaHCO_3$ at 0 °C gave the racemic epoxy ester **4**. Jacobsen hydrolytic kinetic resolution of **4** with H_2O in the presence of 5% (*S*,*S*)-salen-Co catalyst in ether furnished the chiral diol **10** with >95% ee.[11,26] Diol **10** was converted into the

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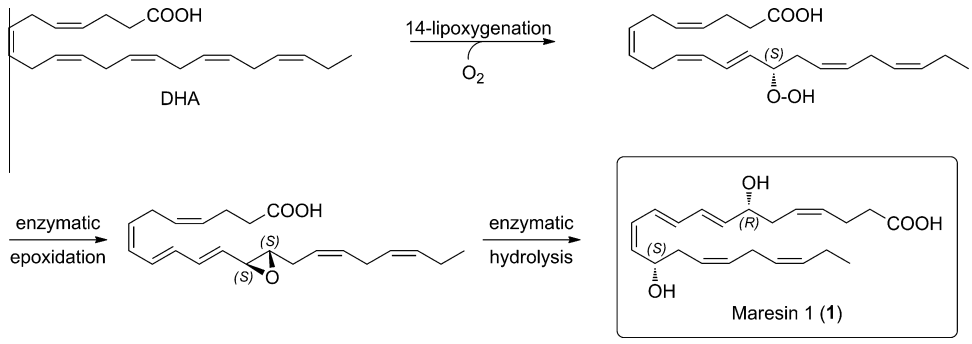


Figure 1. Biosynthesis of Maresin 1.

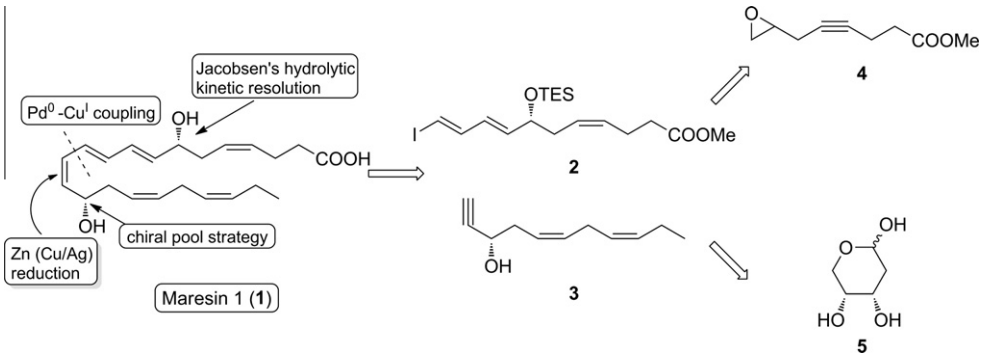
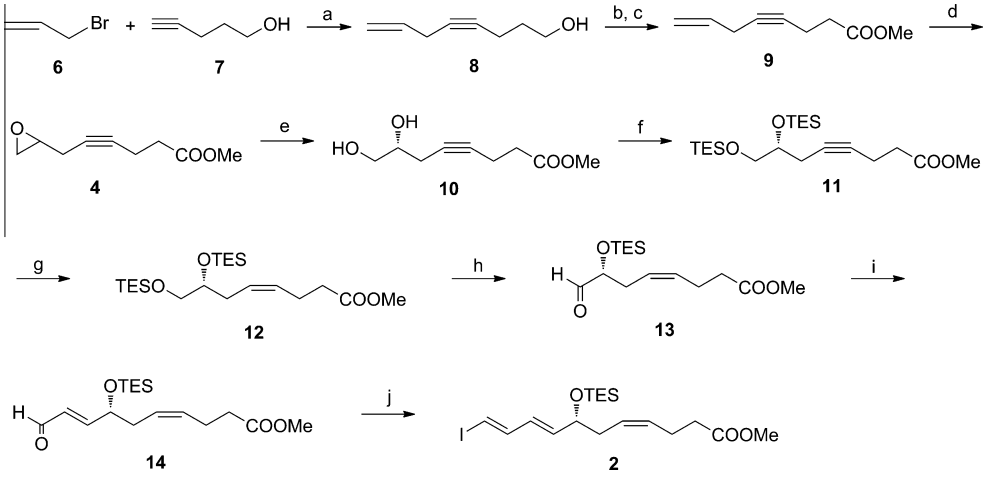


Figure 2. Retrosynthetic approach to Maresin 1.

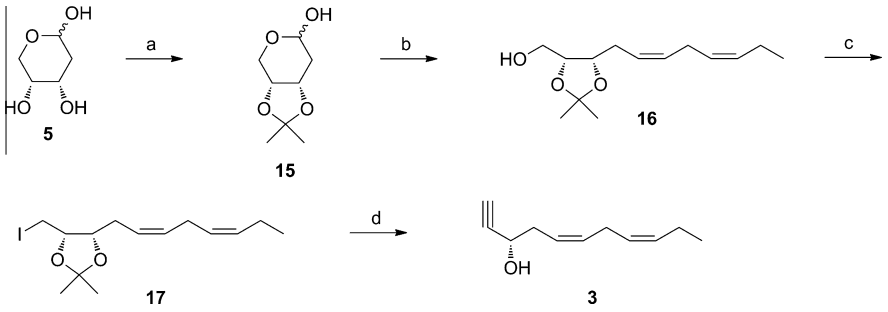


Scheme 1. Reagents and conditions: (a) Na_2SO_3, cat. CuI, K_2CO_3, H_2O, 92%; (b) Jones reagent, acetone, 69%; (c) 10% TMSCl, CH_3OH, 2,2-dimethoxypropane, rt, 90%; (d) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 75%; (e) (*S,S*)-(salen)Co(III)(OAc) catalyst, H_2O, ether, 0 °C to rt, 45%; (f) TESCl, imidazole, Et_3N, DMF, 0 °C to rt, 95%; (g) H_2, Lindlar cat., hexane, 99%; (h) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N, 83%; (i) $Ph_3P{=}CH{-}CHO$, benzene, 70 °C, 43%; (j) $CrCl_2$, CHI_3, THF, 0 °C, 69%.

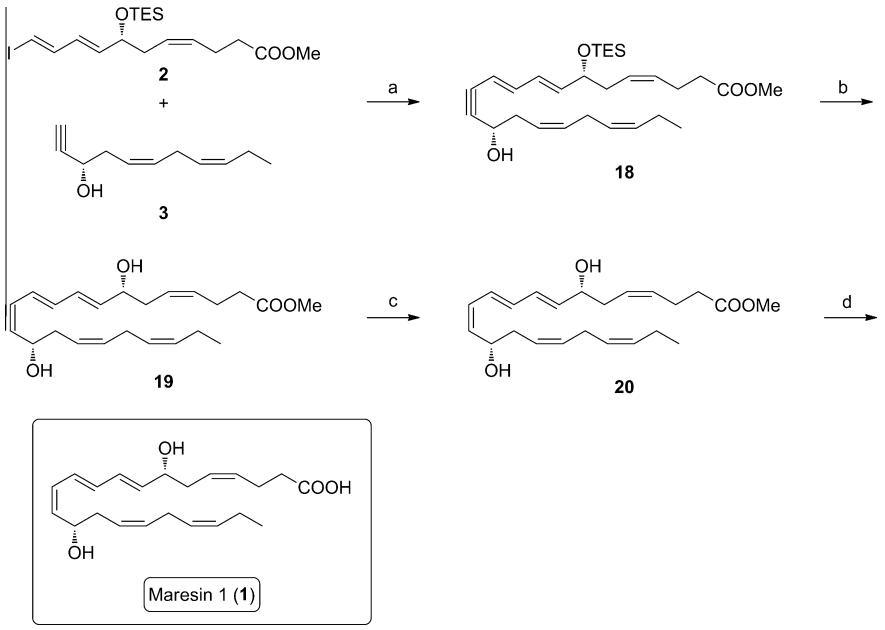
di-TES-ether **11** with 4.1 equiv TESCl in DMF in 95% yield.[11] Lindlar reduction of **11** in hexane produced the (*Z*)-alkene **12** in quantitative yield. Chemoselective oxidation of the primary TES-ether with the Swern reagent produced the aldehyde **13** in 83% yield.[27,28] Wittig homologation of **13** with 2 equiv of triphenylphosphoranyliden-acetaldehyde in benzene at 70 °C gave the α,β-unsaturated aldehyde **14** that was converted into the key intermediate **2** by the Takai olefination ($CrCl_2/CHI_3$) in THF at 0 °C (69% yield).[29]

The C12–C22 chiral fragment **3** was obtained in 4 steps from 2-deoxy-D-ribose (**5**) as outlined in Scheme 2. Isopropylidene protection of **5** with 2-methoxypropene in the presence of a catalytic amount of PPTS in ethyl acetate gave 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**15**) in 50% yield.[30] Wittig reaction of **15** with 2.1 equiv of (Z)-3-(hexen-1-ylidene)triphenylphosphorane,[31] generated in situ from the corresponding phosphonium iodide with BuLi (2 equiv) in THF at −78 °C, produced the *Z,Z*-skipped diene **16** in 81% yield. Compound **16** was converted into the iodide **17** using the method of Samuelson with I_2, Ph_3P, and imidazole in toluene at 60 °C in 82% yield.[32,33] Base induced deprotonation-elimination of **17** with 7 equiv LDA at −78 °C in THF produced directly the key intermediate **3** in 53% isolated yield.[33,34]

The total synthesis of Maresin 1 (**1**) was completed as shown in Scheme 3. Sonogashira coupling of the two key fragments **2** and **3** with a catalytic amount of $Pd(PPh_3)_4$,[35] CuI, and piperidine in benzene at room temperature gave the mono-TES-protected acetylene precursor of Maresin 1 (**18**).[36–38] Mild desilylation with a catalytic



Scheme 2. Reagents and conditions: (a) 2-methoxypropene, PPTS, EtOAc, 0 °C to rt, 50%; (b) (*Z*)-$CH_3CH_2CH{=}CH(CH_2)_2P^+Ph_3I^-$, BuLi, THF, −78 °C to 0 °C, 81%; (c) I_2, Ph_3P, imidazole, toluene, 60 °C, 82%; (d) LDA, THF, −78 °C, 53%.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, piperidine, benzene, rt, 81%; (b) PPTS, CH_3OH, 0 °C, 96%; (c) Zn(Cu/Ag), CH_3OH, H_2O, 40–45 °C, 66%; (d) 1 N LiOH, CH_3OH, H_2O, 0 °C, then satd. NaH_2PO_4, 77%.

amount of PPTS in CH_3OH at 0 °C gave the acetylene precursor of Maresin 1 methyl ester (**19**) in high yield. Attempts to reduce the conjugated triple bond with deactivated Lindlar catalyst produced only over-reduced products. The reduction of the conjugated triple bond with freshly prepared Zn(Cu/Ag) in CH_3OH/H_2O (1:1) at 40–45 °C (16 h) produced Maresin 1 methyl ester (**20**)[39,40] that was purified by HPLC.[41] Mild alkaline hydrolysis of **20** with 1 N LiOH in CH_3OH/H_2O (1:1) at 0 °C followed by acidification with sat. NaH_2PO_4 in the presence of ethyl acetate gave natural Maresin 1 (**1**) (77%). The ^1H and ^{13}C NMR spectra were in accordance with those reported by Inoue.[16] HPLC analysis revealed that the synthesized **1** co-eluted with an authentic sample of Maresin 1 (Cayman Chemical Company).[42]

In summary, a concise total synthesis of Maresin 1 has been achieved,[42] making this anti-inflammatory lipid mediator from docosahexaenoic acid available for further biological and pharmacological testing. The synthesis of other Resolvins and Neuroprotectin D1 will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.143.

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41. HPLC [Zorbax SB-C18, 21.2 mm × 25 cm, 271 nm, CH_3OH/H_2O 70/30, 10 mL/min, tR (*E*, *E*, *E*-isomer) = 61 min, t*R* (*E*, *E*, *Z*-isomer, 20) = 77 min].
42. *Satisfactory spectroscopic data were obtained for all compounds.* Selected physical data: *Compound* ***8***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.9–5.7 (ddt, J = 17.1, 9.9, 5.4 Hz, 1H), 5.3–5.2 (dq, J = 17.1, 1.8 Hz, 1H), 5.1–5.0 (dq, J = 9.9, 1.8 Hz, 1H), 3.8–3.7 (m, 2H), 3.0–2.8 (m, 2H), 2.4–2.2 (tt, J = 6.9, 2.4 Hz, 2H), 1.8–1.7 (quint, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 133.19, 115.71, 81.84, (C5 overlaps with $CDCl_3$ signals), 62.00, 31.58, 23.08, 15.43. *Compound* ***9***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.9–5.7 (ddt, J = 17.1, 9.9, 5.1 Hz, 1H), 5.3–5.2 (dq, J = 17.1, 1.8 Hz, 1H), 5.1–5.0 (dq, J = 9.9, 1.8 Hz, 1H), 3.7 (s, 3H), 2.9–2.8 (m, 2H), 2.5–2.4 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.45, 133.00, 115.66, 80.60, 77.50, 51.61, 33.78, 22.98, 14.77. *Compound* ***4***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.7 (s, 3H), 3.1–3.0 (m, 1H), 2.8–2.7 (dd, J = 4.8, 3.9 Hz, 1H), 2.7–2.6 (dd, J = 4.8, 2.7 Hz, 1H), 2.6–2.3 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.42, 80.59, 75.07, 51.60, 50.03, 46.25, 33.57, 22.38, 14.65. *Compound* ***11***: $[\alpha]_D^{25}$ = +2.6 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.8–3.7 (quint, J = 5.7 Hz, 1H), 3.7 (s, 3H), 3.6–3.4 (2 dd ABsystem, J = 9.9, 5.7 Hz, 2H), 2.6–2.4 (m, 4H), 2.5–2.3 (ddt ABsystem, J = 16.5, 5.7, 1.8 Hz, 1H), 2.3–2.1 (ddt ABsystem, J = 16.5, 6.0, 2.1 Hz, 1H), 1.0–0.9 (2 t, J = 7.8 Hz, 18H), 0.7–0.5 (2 q, J = 7.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.49, 79.37, 78.07, 72.26, 66.28, 51.60, 33.72, 24.58, 14.82, 6.77 (3C), 6.69 (3C), 4.98 (3C), 4.41 (3C). *Compound* ***12***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.3 (m, 2H), 3.7–3.6 (m, 1H), 3.6 (s, 3H), 3.5–3.4 (dd ABsystem, J = 9.9, 5.7 Hz, 1H), 3.4–3.3 (dd ABsystem, J = 9.9, 6.3 Hz, 1H), 2.6–2.1 (m, 6H), 1.0–0.9 (2 t, J = 8.1 Hz, 18H), 0.7–0.5 (2 q, J = 7.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.59, 129.18, 127.34, 73.02, 66.63, 51.45, 34.07, 32.19, 22.97, 6.85 (3C), 6.74 (3C), 5.01 (3C), 4.41 (3C). *Compound* ***14***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6–9.5 (d, J = 8.1 Hz, 1H), 6.8–6.7 (dd, J = 15.6, 4.5 Hz, 1H), 6.4–6.2 (ddd, J = 15.6, 8.1, 1.5 Hz, 1H), 5.5–5.3 (m, 2H), 4.5–4.3 (m, 1H), 3.6 (s, 3H), 2.4–2.2 (m, 6H), 0.9 (t, J = 7.8 Hz, 9H), 0.6 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.44, 173.32, 159.12, 130.93, 130.64, 125.37, 71.35, 51.52, 35.37, 33.79, 22.97, 6.74 (3C), 4.84 (3C). *Compound* ***2***: ^{1}H NMR (C_6D_6, 300 MHz): δ 7.0–6.9 (dd, J = 14.4, 10.8 Hz, 1H), 6.1–5.9 (m, 2H), 5.7–5.4 (m, 3H), 4.2–4.0 (m, 1H), 3.4 (s, 3H), 2.5–2.2 (m, 6H), 1.1 (t, J = 7.8 Hz, 9H), 0.7 (q, J = 7.8 Hz, 6H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ 173.15, 145.40, 138.33, 130.61, 129.85, 127.22, 79.51, 73.03, 51.46, 36.91, 34.44, 23.82, 7.55 (3C), 5.84 (3C). *Compound* ***16***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.2 (m, 4H), 4.3–4.1 (m, 2H), 3.7–3.5 (m, 2H), 2.8–2.7 (br t, J = 7.0 Hz, 2H), 2.5–2.2 (m, 2H), 2.1–1.9 (quint, J = 7.5 Hz, 2H), 2.0–1.9 (br t, J = 6.0 Hz, 1H), 1.5 (s, 3H), 1.3 (s, 3H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.27, 130.86, 126.57, 124.78, 108.18, 77.82, 76.70, 61.68, 28.09, 27.43, 25.77, 25.38, 20.54, 14.17. *Compound* ***17***: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.2 (m, 4H), 4.4–4.2 (m, 1H), 4.2–4.0 (m, 1H), 3.2–3.1 (m, 2H), 2.8 (br t, J = 7.0 Hz, 2H), 2.4–2.3 (br t, J = 6.5 Hz, 2H), 2.1–2.0 (quint, J = 7.5 Hz, 2H), 1.5 (s, 3H), 1.3 (s, 3H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.32, 130.98, 126.51, 124.50, 108.53, 78.26, 77.55, 28.35, 27.55, 25.84, 25.66, 20.59, 14.19, 3.56. *Compound* ***3***: $[\alpha]_D^{20}$ = −31.7 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.2 (m, 4H), 4.5–4.3 (qd, J = 6.3, 2.1 Hz, 1H), 2.9–2.7 (m, 2H), 2.6–2.4 (m, 2H), 2.4 (d, J = 2.1 Hz, 1H), 2.1–2.0 (m, 2H), 1.9 (d, J = 6.3 Hz, 1H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 132.58, 132.35, 126.65, 123.35, 84.46, 73.00, 61.80, 35.55, 25.79, 20.58, 14.17. *Compound* ***19***: ^{1}H NMR (C_6D_6, 300 MHz): δ 6.8–6.6 (dd, J = 15.3, 11.1 Hz, 1H), 6.4–6.2 (dd, J = 15.3, 11.1 Hz, 1H), 5.8–5.6 (m, 4H), 5.6–5.4 (m, 4H), 4.5 (td, J = 6.3, 1.8 Hz, 1H), 4.1–4.0 (br q, J = 6.3 Hz, 1H), 3.4 (s, 3H), 2.9 (br t, J = 5.7 Hz, 2H), 2.6 (br t, J = 6.3 Hz, 2H), 2.4–2.0 (m, 8H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ 173.47, 142.31, 139.70, 132.71, 132.37, 131.43, 129.52, 127.84, 127.06, 125.11, 111.50, 94.00, 84.82, 71.77, 63.23, 51.54, 36.74, 36.06, 34.22, 26.62, 23.57, 21.36, 14.86. UV (EtOH) λ_{max} 267, 279 nm. *Compound* ***20***: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.6–6.4 (m, 1H), 6.3–6.2 (m, 2H), 6.1–5.9 (t, J = 11.1 Hz, 1H), 5.8–5.6 (dd, J = 14.1, 6.3 Hz, 1H), 5.5–5.2 (m, 7H), 4.6–4.4 (m, 1H), 4.2–4.0 (m, 1H), 3.6 (s, 3H), 2.9 (d, J = 4.5 Hz, 1H), 2.8 (d, J = 4.5 Hz, 1H), 2.8–2.7 (br t, J = 6.4 Hz, 2H), 2.4–2.1 (m, 8H), 2.1–2.0 (quint, J = 7.5 Hz, 2H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 173.88, 138.17, 135.15, 134.12, 132.34, 130.69, 130.47, 130.05, 129.42, 128.36, 127.73, 127.21, 125.96, 71.76, 67.66, 51.53, 36.00, 35.73, 34.05, 26.01, 23.27, 20.80, 14.17. UV (EtOH) λ_{max} 262, 271, 282 nm. *Compound* ***1***: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.7–6.5 (m, 1H), 6.4–6.2 (m, 2H), 6.1–6.0 (t, J = 11.1 Hz, 1H), 5.8–5.7 (dd, J = 14.1, 6.6 Hz, 1H), 5.6–5.2 (m, 7H), 4.6–4.5 (m, 1H), 4.2–4.1 (br q, J = 6.6 Hz, 1H), 2.8 (br t, J = 6.3 Hz, 2H), 2.5–2.2 (m, 8H), 2.2–2.0 (quint, J = 7.5 Hz, 2H), 1.0 (t, J = 7.5 Hz, 3H). ^{13}C NMR (CD_3OD, 75.5 MHz): δ C1 not observed, 138.00, 134.95, 134.84, 132.81, 131.40, 131.35, 131.15, 130.58, 128.90, 128.20, 127.42, 126.12, 72.96, 68.57, 36.53, 36.29, 35.15, 26.64, 24.17, 21.48, 14.59. UV (EtOH) λ_{max} 262, 271, 282 nm. HPLC-UV: Hypersil-ODS, 100 × 2.1 mm, 271 nm, CH_3OH/H_2O (0.1% formic acid) 50/50 to 70/30, 0.2 mL/min, t*R* = 17.2 min [synthesized **1** co-eluted with an authentic sample of Maresin 1 (Cayman Chemical Company)]. HPLC/MS/MS (*m*/*z*): 359.3 $[M-H]^-$.

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Total synthesis of the anti-inflammatory lipid mediator Resolvin E2

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ABSTRACT

The total synthesis of Resolvin E2, an endogenous lipid mediator of the resolution of inflammation derived from eicosapentaenoic acid, has been achieved. The chiral hydroxy-groups at C5 and C18 were generated in a simple, efficient, and environmentally friendly manner via an asymmetric Noyori transfer hydrogenation in water using sodium formate as a reducing agent. Pd^0/Cu^I Sonogashira couplings of the three key fragments and Zn(Cu/Ag) reduction completed the synthesis of Resolvin E2.

Inflammation plays a key role in asthma, arthritis, atherosclerosis, and Alzheimer's disease among others.[1–4] The beneficial effects of ω-3 fatty acids (fish oil) in these diseases could be addressed in part by shifting the formation of pro-inflammatory leukotrienes derived from arachidonic acid to the less inflammatory leukotrienes derived from eicosapentaenoic acid.[5] Recently, Serhan et al. have identified in vivo a series of lipid mediators of the resolution of inflammation derived from eicosapentaenoic acid (Resolvins E1 and E2) and from docosahexaenoic acid (Resolvins D1, D2, D3, D4, D5, D6, Neuroprotectin D1 and Maresin).[6,7] These endogenous Resolvins are potent anti-inflammatory lipid mediators.[8–16]

The growing interest to study the pharmacological properties of the Resolvins combined with the limited availability from natural sources requires their preparation by total syntheses.[17–25]

Two independent syntheses of Resolvin E2 by Inoue et al. and Kobayashi et al. have been recently reported. Inoue utilized a cyclobutene lactone approach for the chiral hydroxy-groups whereas Kobayashi generated the chiral centers by Sharpless kinetic resolution.[19,21]

In this communication, we wish to report a short total synthesis of Resolvin E2 [RvE2; (5*S*,6*E*,8*Z*,11*Z*,14*Z*,16*E*,18*R*)-5,18-dihydroxy-6,8,11,14,16-eicosapentaenoic acid; (**1**)]. As shown in Figure 1, RvE2 was prepared from the readily available key intermediates **2**, **3**, and **4**. We have successfully employed a similar strategy for the synthesis of RvD6.[25] Intrigued by recent reports that the asymmetric Noyori transfer hydrogenation could be carried out in water; we investigated this protocol to generate both chiral centers of RvE2 in a simple, efficient, and environmentally friendly manner.[26–29]

The C1–C7 fragment **2** was prepared in five steps as outlined in Scheme 1. Reduction of the ketone **5**,[23,30] in H_2O/ethyl acetate in the presence of a catalytic amount of the phase transfer catalyst hexadecyl trimethyl ammonium bromide (CTABr) using the Noyori RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) precatalyst (0.035 equiv) with sodium formate as a reducing agent, produced the chiral intermediate **6** with >93% ee as determined by chiral HPLC [Chiracel OD, hexane/*i*-PrOH 90:10, 0.6 mL/min, 210 nm, t_R = 8.5 min (*R*-isomer) and t_R = 9.6 min (*S*-isomer, **6**)].[31,32] TMS desilylation of **6** with 1.2 equiv K_2CO_3/Na_2SO_4 in CH_3OH gave cleanly the terminal acetylene **7**. Under these conditions no ester cleavage was observed.[33] Protection of **7** with TBSCl in DMF produced the silyl ether **8** in quantitative yield. Hydrostannylation of **8** with excess tributyltin hydride at 130 °C in the presence of a catalytic amount of AIBN produced the *trans*-vinyl tin compound **9** in a 74% yield. Excess of tributyltin hydride was removed in high vacuo. The key intermediate **2** was obtained from **9** by reaction with iodine in ether at 0 °C. On large scale the removal of tributyltin iodide by flash chromatography became a problem due to its similar solubility and chromatographic behavior with **2**. Corey[34] and Harrowven[35] reported effective procedures to remove organotin halides from reaction mixtures. A combination of both methods, stirring the reaction mixture with K_2CO_3/silica gel in hexane followed by simple filtration, produced a tin-free hexane solution of **2**. Neither K_2CO_3 nor silica gel alone was capable to remove the tin impurities.

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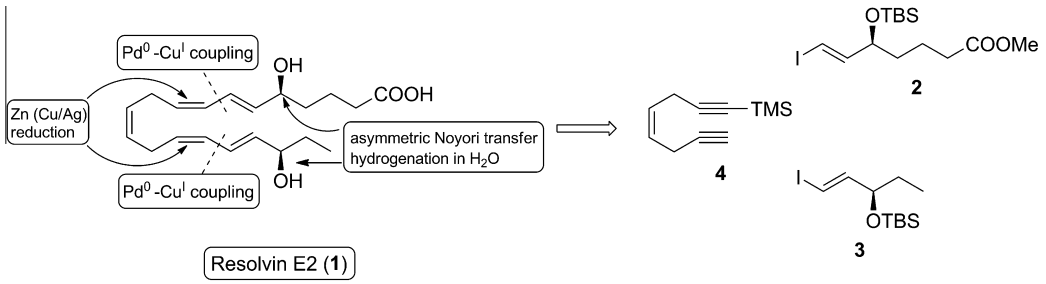
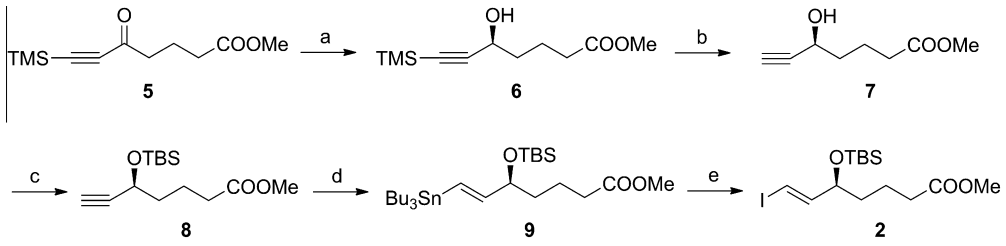
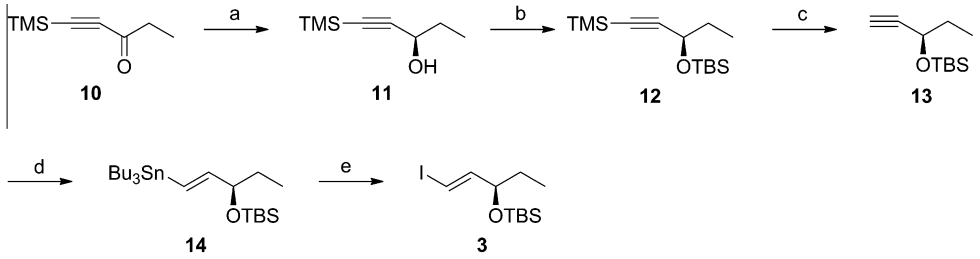


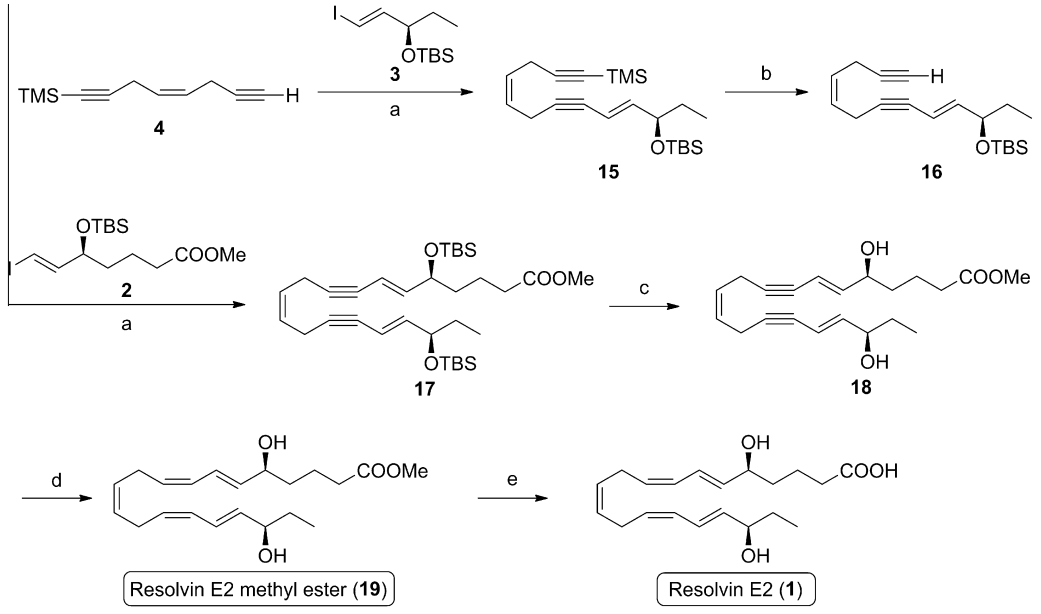
Figure 1. Retrosynthetic approach to RvE2.



Scheme 1. Reagents and conditions: (a) RuCl[(*S,S*)-TsDPEN](*p*-cymene), CTABr, HCOONa, H_2O, EtOAc, rt, 65%; (b) K_2CO_3, Na_2SO_4, CH_3OH, rt, 85%; (c) TBSCl, imidazole, DMF, 0 °C to rt, 99%; (d) $(Bu)_3SnH$, AIBN, 130 °C, 74%; (e) I_2, ether, 0 °C, 90%.



Scheme 2. Reagents and conditions: (a) RuCl[(*R,R*)-TsDPEN](*p*-cymene), CTABr, HCOONa, H_2O, EtOAc, rt; (b) TBSCl, imidazole, DMF, 0 °C to rt, 84% (two-steps, a and b); (c) $AgNO_3$, CH_3OH, H_2O, NaCN, 0 °C; (d) $(Bu)_3SnH$, AIBN, 130 °C, 84%; (e) I_2, ether, 0 °C, 89%.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, *n*-$PrNH_2$, benzene, rt, 58%; (b) $AgNO_3$, CH_3OH, H_2O, NaCN, 0 °C; (c) MeCOCl, CH_3OH, 0 °C to rt.; (d) Zn(Cu/Ag), CH_3OH, H_2O, 50 °C; (e) 1 N LiOH, H_2O, CH_3OH, 0 °C, then H^+ (NaH_2PO_4 saturated), 79%.

The chiral key intermediate **3** was obtained from 1-(trimethylsilyl)-1-pentyn-3-one (**10**)[36] via a transfer hydrogenation with the Noyori RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) precatalyst (0.035 equiv) as outlined in Scheme 2. The asymmetric reduction was carried out in H_2O, as described above for **6**, producing the chiral intermediate **11** in a fast reaction with >93.7% ee as determined by chiral HPLC [Chiracel OF, hexane/*i*-PrOH 99.7:0.3, 1.5 mL/min, 210 nm, t_R = 9.7 min (*S*-isomer) and t_R = 11.2 min (*R*-isomer, **11**)]. The same reduction could be carried out in *i*-PrOH but the active Noyori catalyst had to be used, in addition to carefully controlled conditions and longer reaction times, to obtain a higher ee.[36] Protection of **11** with TBSCl in DMF at 0 °C to rt produced the silyl ether derivatives **12** in an 84% combined yield (two-steps). TMS desilylation using $AgNO_3$ followed by NaCN work-up gave **13**.[37,38] Hydrostannylation of **13** with excess tributyltin hydride at 130 °C in the presence of a catalytic amount of AIBN produced the *trans*-vinyl tin compound **14** in an 84% yield. The tin-iodine exchange was accomplished by treating **14** with an ether solution of iodine at 0 °C. Work-up with sat. $Na_2S_2O_3$ followed by flash chromatography gave the key intermediate **3**.

We have recently described the synthesis of the C8–C15 fragment **4** in two-steps by CuI catalyzed coupling of *cis*-1,4-dibromo-2-butene with excess trimethylsilyl acetylene followed by $AgNO_3$ catalyzed monodesilylation.[25]

The skeleton of RvE2 was assembled from the key intermediates **2**, **3**, and **4** as outlined in Scheme 3. Pd^0/Cu^I Sonogashira coupling of **3** with **4** produced compound **15** (58%).[39] Desilylation using $AgNO_3$ followed by NaCN work-up gave **16**, that was used without further purification in the second Sonogashira coupling with **2** to give the diacetylene precursor of RvE2 methyl ester (**17**).

The synthesis was completed via deprotection of the TBS groups of compound **17** with catalytic HCl, generated in situ from acetyl chloride in absolute methanol at 0 °C to rt, to give **18**. Zn(Cu/Ag) reduction of **18** in CH_3OH/H_2O at 50 °C (16 h) produced cleanly RvE2 methyl ester (**19**).[40,41] Mild alkaline hydrolysis of **19** with LiOH in CH_3OH/H_2O at 0 °C followed by acidification with sat. NaH_2PO_4 in the presence of ethyl acetate gave RvE2 (**1**). The ^1H and ^{13}C NMR spectra and the specific rotation were in accordance with those reported.[19,21]

In summary, a concise total synthesis of RvE2 has been achieved,[42] making this anti-inflammatory lipid mediator from eicosapentaenoic acid available for further biological and pharmacological testing. The synthesis of other Resolvins, Maresin, and Neuroprotectin D1 will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.136.

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42. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **6**: $[\alpha]_D^{25} = -6.0$ (c 2.1, $CHCl_3$) [lit.[43] $[\alpha]_D^{19} = -6.4$ (c 1.4, CH_2Cl_2)]. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.4–4.3 (m, 1H), 3.6 (s, 3H), 2.4–2.3 (t, *J* = 7.0 Hz, 2H), 1.9 (br s, 1H), 1.8–1.6 (m, 4H), 0.2 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.84, 106.36, 89.71, 62.40, 51.52, 36.93, 33.55, 20.55, −0.17 (3C). Compound **7**: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.4–4.3 (m, 1H), 3.6 (s, 3H), 2.5–2.4 (d, *J* = 2.1 Hz, 1H), 2.4–2.3 (t, *J* = 7.0 Hz, 2H), 2.2–2.1 (br s, 1H), 1.9–1.6 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.80, 84.63, 73.09, 61.86, 51.48, 36.91, 33.55, 20.46. Compound **8**: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.4–4.3 (td, *J* = 6.0, 2.1 Hz, 1H), 3.6 (s, 3H), 2.4–2.3 (d, *J* = 2.1 Hz, 1H), 2.3 (t, *J* = 7.2 Hz, 2H), 1.8–1.6 (m, 4H), 0.9 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.80, 85.21, 72.29, 62.40, 51.42, 37.79, 33.68, 25.75 (3C), 20.62, 18.17, −4.58, −5.10. Compound **9**: ^1H NMR ($CDCl_3$, 300 MHz): δ 6.0 (d, *J* = 19.0 Hz, 1H), 5.9 (dd, *J* = 19.0, 5.7 Hz, 1H), 4.1–4.0 (br q, *J* = 5.7 Hz, 1H), 3.6 (s, 3H), 2.3 (t, *J* = 7.3 Hz, 2H), 1.7–1.2 (m, 16H), 1.0–0.8 (m, 15H), 0.9 (s, 9H), 0.1–0.0 (2s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.95, 151.56, 127.15, 76.34, 51.27, 37.44, 34.14, 29.13 (3C), 27.21 (3C), 25.94 (3C), 20.89, 18.29, 13.60 (3C), 9.56 (3C), −4.25, −4.76. Compound **2**: ^1H NMR ($CDCl_3$, 300 MHz): δ 6.5–6.4 (dd, *J* = 14.4, 6.0 Hz, 1H), 6.2 (dd, *J* = 14.4, 1.2 Hz, 1H), 4.1–4.0 (qd, *J* = 6.0, 1.2 Hz, 1H), 3.6 (s, 3H), 2.3 (t, *J* = 7.3 Hz, 2H), 1.7–1.4 (m, 4H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.73, 148.81, 75.94, 74.76, 51.42, 36.78, 33.87, 25.79 (3C), 20.27, 18.15, −4.55, −4.92. Compound **11**: $[\alpha]_D^{25} = +5.2$ (c 1.0, $CHCl_3$) [lit.[36] $[\alpha]_D^{19} = +6.0$ (c 2.0, $CHCl_3$)]. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.3 (t, *J* = 6.4 Hz, 1H), 1.8–1.6 (m, 3H), 1.0 (t, *J* = 7.5 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 106.69, 89.44, 64.15, 30.83, 9.32, −0.13 (3C). Compound **12**: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.3–4.2 (t, *J* = 6.4 Hz, 1H), 1.7–1.6 (m, 2H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H), 0.9 (s, 9H), 0.13 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 107.82, 88.39, 64.74, 31.68, 25.84 (3C), 18.30, 9.65, −0.15 (3C), −4.47, −4.90. Compound **13**: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.3–4.2 (td, *J* = 6.3, 2.1 Hz, 1H), 2.4–2.3 (d, *J* = 2.1 Hz, 1H), 1.8–1.6 (m, 2H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H), 0.9 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 85.61, 71.84, 64.07, 31.73, 25.79 (3C), 18.23, 9.43, −4.58, −5.05. Compound **3**: ^1H NMR ($CDCl_3$, 300 MHz): δ 6.5 (dd, *J* = 14.4, 6.0 Hz, 1H), 6.2 (dd, *J* = 14.4, 1.2 Hz, 1H), 4.0 (qd, *J* = 6.0, 1.2 Hz, 1H), 1.6–1.4 (m, 2H), 0.9 (s, 9H), 0.9–0.8 (t,

J = 7.5 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 149.12, 76.28, 75.46, 30.38, 25.83 (3C), 18.22, 9.12, −4.57, −4.88. Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.0 (dd, *J* = 15.9, 5.4 Hz, 1H), 5.7–5.5 (m, 1H), 5.6–5.4 (m, 2H), 4.1–4.0 (m, 1H), 3.1–2.9 (m, 4H), 1.6–1.4 (m, 2H), 0.9 (s, 9H), 0.9–0.8 (t, *J* = 7.5 Hz, 3H), 0.1 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.40, 126.39, 125.89, 109.11, 104.38, 87.38, 84.87, 79.08, 73.82, 30.80, 25.91 (3C), 18.41, 18.25, 17.96, 9.16, 0.07 (3C), −4.45, −4.80. Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.0 (dd, *J* = 15.9, 5.4 Hz, 1H), 5.7–5.4 (m, 3H), 4.1–4.0 (m, 1H), 3.1–2.9 (m, 4H), 2.0–1.9 (t, *J* = 2.7 Hz, 1H), 1.6–1.4 (m, 2H), 0.9 (s, 9H), 0.9–0.8 (t, *J* = 7.5 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.49, 126.55, 125.59, 108.91, 87.17, 81.94, 79.09, 73.71, 68.42, 30.73, 25.87 (3C), 18.23, 17.87, 16.88, 9.22, −4.49, −4.85. Compound **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.1–5.9 (2 dd, *J* = 15.9, 6.0 Hz, 2H), 5.7–5.4 (m, 4H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.1–3.0 (m, 4H), 2.3–2.2 (t, *J* = 7.5 Hz, 2H), 1.7–1.5 (m, 2H), 1.6–1.4 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.9–0.8 (t, *J* = 7.5 Hz, 3H), 0.02 (s, 6H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.80, 145.40, 145.02, 126.17, 126.05, 109.42, 109.02, 87.75, 87.37, 79.05, 78.85, 73.76, 72.29, 51.35, 37.26, 34.03, 30.76, 25.88 (6C), 20.42, 18.22, 18.18, 17.90 (2C), 9.18, −4.44, −4.47, −4.83 (2C). Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.1–6.0 (2 dd, *J* = 15.9, 6.3 Hz, 2H), 5.7–5.6 (m, 2H), 5.6–5.5 (m, 2H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.1–3.0 (m, 4H), 2.3 (t, *J* = 7.5 Hz, 2H), 1.8–1.4 (m, 6H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.86, 144.58, 144.34, 126.17, 126.07, 110.59, 110.39, 88.37, 88.06, 78.74, 78.61, 73.63, 71.86, 51.44, 36.33, 33.78, 29.96, 20.68, 17.86 (2C), 9.43. Compound **19**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.7–6.5 (dd, *J* = 15.3, 11.1 Hz, 2H), 6.1–5.9 (br t, *J* = 10.8 Hz, 2H), 5.8–5.6 (2 dd, *J* = 15.3, 6.3 Hz, 2H), 5.5–5.3 (m, 4H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.2 (br d, *J* = 4.8 Hz, 1H), 3.1 (br d, *J* = 4.5 Hz, 1H), 3.1–2.9 (m, 4H), 2.4–2.3 (t, *J* = 7.5 Hz, 2H), 1.8–1.4 (m, 6H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.90, 138.55, 138.47, 130.50, 130.30, 129.40, 129.31, 129.09, 129.04, 125.67, 125.63, 74.00, 72.27, 51.93, 37.59, 34.52, 31.21, 26.88 (2C), 21.87, 10.10. Compound **1**: $[\alpha]_D^{25}$ = −3 (c 0.23, CH_3OH) [lit.[21] $[\alpha]_D^{21}$ = −4 (c 0.056, CH_3OH), lit.[19] $[\alpha]_D^{24}$ = −2.1 (c 0.25, CH_3OH)]. ^{1}H NMR (CD_3OD, 300 yMHz): δ 6.7–6.5 (2 ddt, *J* = 15.3, 11.1, 1.2 Hz, 2H), 6.1–5.9 (br t, *J* = 11.1 Hz, 2H), 5.7–5.6 (2 dd, *J* = 15.3, 6.8 Hz, 2H), 5.5–5.3 (m, 4H), 4.2–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.1–2.9 (m, 4H), 2.3 (t, *J* = 7.2 Hz, 2H), 1.8–1.4 (m, 6H), 0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 177.42, 137.71 (2C), 130.64, 130.47, 129.47, 129.41, 129.12 (2C), 126.38 (2C), 74.68, 72.90, 37.77, 34.84, 31.22, 26.99 (2C), 22.19, 10.12. UV (EtOH) λ_{max} 232 nm. HPLC/API-ES/MS [Hypersil-ODS, 100 × 2.1 mm, CH_3OH/H_2O 65/35 (0.1% formic acid), 0.2 mL/min, t_R = 5.1 min] (*m*/*z*): 357.3 $[M+Na]^+$.

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First total synthesis of the anti-inflammatory lipid mediator Resolvin D6

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ABSTRACT

The first total synthesis of Resolvin D6, an endogenous lipid mediator of resolution of inflammation derived from docosahexaenoic acid, has been achieved. The chiral hydroxy-groups at C4 and C17 were generated via an asymmetric Noyori transfer hydrogenation and a Sharpless catalytic asymmetric epoxidation, respectively. A mild copper catalyzed coupling of *cis*-1,4-dibromo-2-butene with TMS-acetylene generated the C7–C14 fragment. Pd^0/Cu^I Sonogashira couplings and Zn(Cu/Ag) reduction completed the synthesis of Resolvin D6.

The health benefits of ω-3 fatty acids are well documented,[1] including their effects on neutrophil function and leukotriene generation in humans.[2] In 2002, Serhan et al. discovered that the enzymatic metabolism of the two major ω-3 fatty acids of fish oil (docosahexaenoic and eicosapentaenoic acids) produced the Resolvins (resolution phase interaction products) in vivo.[3] These ω-3 fatty acid metabolites are powerful anti-inflammatory and immunoregulatory lipid mediators. The protective role in chronic inflammatory diseases as well as sepsis is currently explored.[4–11]

Their low availability from natural sources prompted us to prepare the Resolvins by total synthesis in order to evaluate their biological and pharmacological properties. We have previously reported the total syntheses of Resolvins D2 and D5.[12,13] Later on syntheses of Resolvins E1 and E2, Protectin D1 and Maresin have been described.[14–20]

In this communication, we wish to report the first total synthesis of Resolvin D6 [RvD6; (4*S*,5*E*,7*Z*,10*Z*,13*Z*,15*E*,17*S*,19*Z*)-4,17-dihydroxy-5,7,10,13,15,19-docosahexaenoic acid; (**1**)]. As shown in Figure 1, RvD6 was prepared from the key intermediates **2**, **3**, and **4**. The chiral center at C4 was obtained via Noyori transfer hydrogenation, using the Ru[(*S*,*S*)-TsDPEN](*p*-cymene) catalyst, whereas the chiral center at C17 was prepared via Sharpless asymmetric epoxidation.

The fragment C1–C6 was prepared from commercial methyl 4-chloro-4-oxobutyrate (**5**) and bis(trimethylsilyl)acetylene (**6**) as outlined in Scheme 1. Alkynylation using 10% $InBr_3$ in CH_2Cl_2 afforded the intermediate **7** in 94% yield.[21] Asymmetric transfer hydrogenation of **7** in *i*-PrOH produced the chiral intermediate **8** with >95% ee as determined by chiral HPLC (Chiracel OF, hexane/*i*-PrOH 95:5).[22,23] TMS desilylation of **8** with $KF{\cdot}2H_2O$ in DMF in the presence of a catalytic amount of 18-crown-6 gave cleanly the terminal acetylene **9**. Protection of **9** with TBSCl in DMF produced the silyl ether **10**. Free radical addition with excess tributyltin hydride at 130 °C in the presence of a catalytic amount AIBN produced the *trans*-vinyl tin compound **11** in 63% combined yield (three-steps). The key intermediate **2** was obtained from **11** by reaction with iodine in ether at 0 °C (93% yield).

The C15–C22 chiral fragment **3** was prepared from propargyl alcohol (**12**) and 1-bromo-2-pentyne (**13**) according to the method of Eiter et al. (CuI, DBU, and HMPA) to afford 2,5-octadiyn-1-ol (**14**) as outlined in Scheme 2.[24] Selective reduction of the propargylic triple bond with $LiAlH_4$ in ether afforded (*E*)-2-octen-5-yn-1-ol (**15**) in 70% yield. Sharpless cat. AE of **15** gave the crystalline epoxy alcohol **16**. Recrystallization from hexane/ethyl acetate at 4 °C gave **16** with >98% ee, as determined by Chiral HPLC (Chiracel OD, hexane/*i*-PrOH 95:5).[25–27] Lindlar reduction of **16** in hexane afforded crystalline **17**. Using the method of Samuelson,[28] **17** was converted to the iodo epoxide **18**. The crucial step to transform the 1-iodo-2,3-epoxide **18** into (1*E*,3*S*,5*Z*)-1-iodo-1,5-octadien-3-ol (**19**) was achieved following Nakata's protocol (NaHMDS in DMF at −60 °C).[29,30] Standard protection of **19** with TBSCl in DMF gave the second key intermediate **3** in 67% yield.

The synthesis of the C7–C14 fragment **4** was accomplished in two-steps as outlined in Scheme 3. According to the method of Bieber et al.[31] CuI catalyzed coupling of freshly distilled *cis*-1,4-dibromo-2-butene (**20**)[32] with excess trimethylsilyl acetylene (**21**) in DMF at room temperature gave **22** in 34% isolated yield. The ^1H

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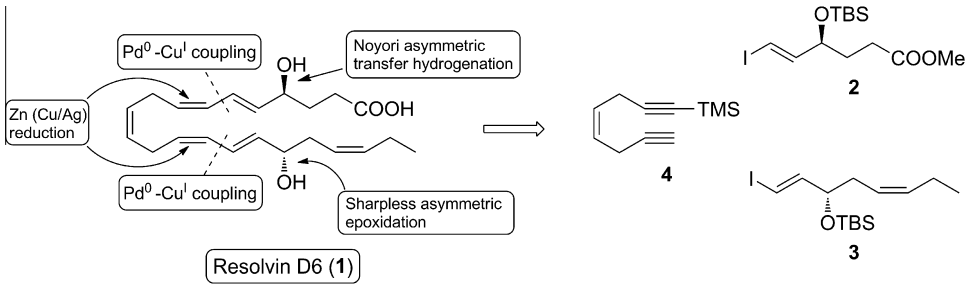
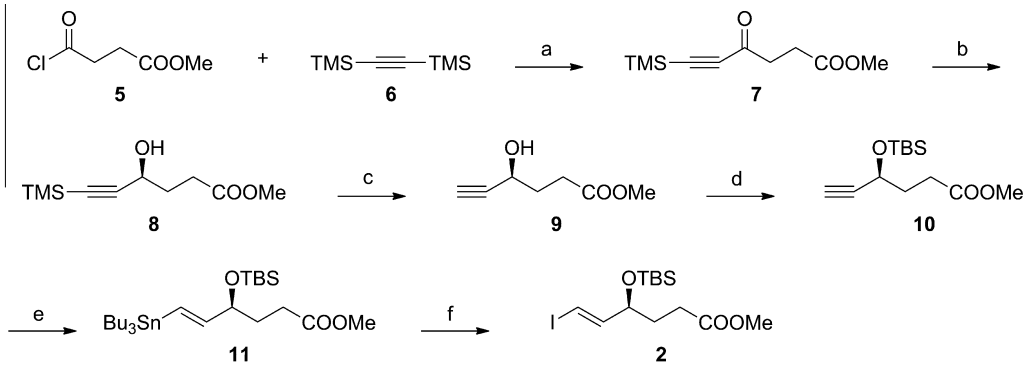
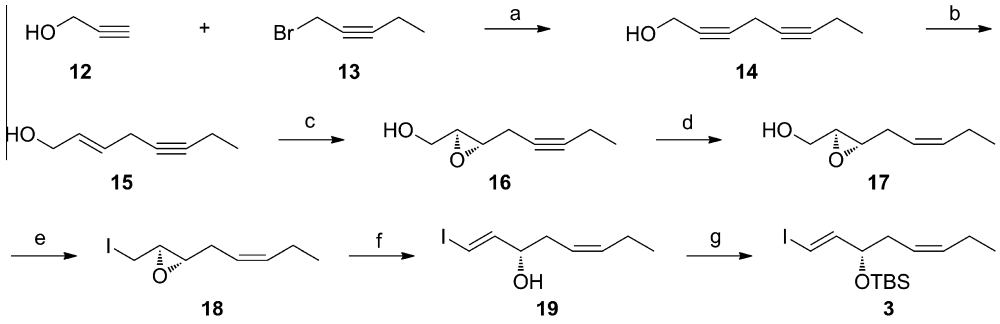


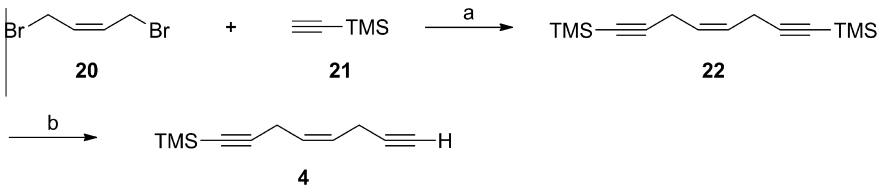
Figure 1.



Scheme 1. *Reagents and conditions:* (a) 10% $InBr_3$, CH_2Cl_2, 0 °C to rt; (b) Ru[(*S*,*S*)-TsDPEN](*p*-cymene), *i*-PrOH, rt; (c) KF·$2H_2O$, 18-crown-6, DMF, rt; (d) TBSCl, imidazole, DMF, 0 °C to rt; (e) $(Bu)_3SnH$, AIBN, 130 °C; and (f) I_2, ether, 0 °C.



Scheme 2. *Reagents and conditions:* (a) DBU, CuI, HMPA, THF; (b) $LiAlH_4$, ether, 0 °C to rt; (c) L(+)DMT, $Ti(OiPr)_4$, TBHP, molecular sieves 4 Å, CH_2Cl_2; (d) H_2, Lindlar cat., Et_3N, hexane; (e) I_2, Ph_3P, imidazole, *i*-Pr_2EtN, CH_3CN, ether; (f) NaHMDS, DMF, −60 °C; and (g) TBSCl, imidazole, DMF.

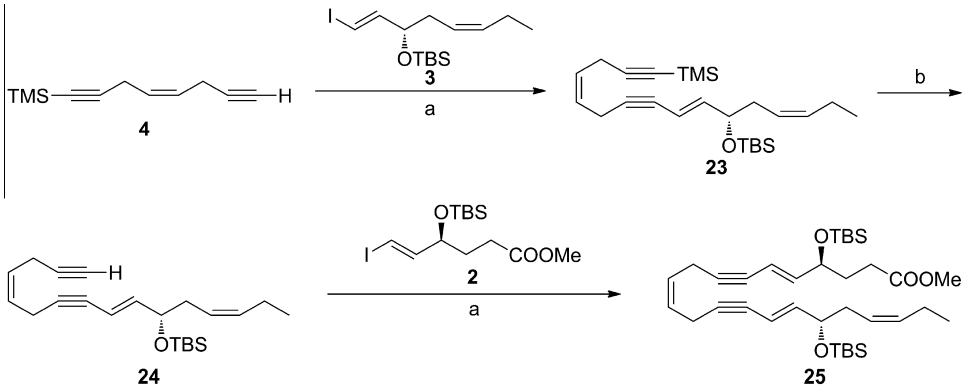


Scheme 3. *Reagents and conditions:* (a) CuI, Na_2SO_3, K_2CO_3, DMF, rt; (b) $AgNO_3$, CH_3OH, H_2O, NaCN, 0 °C.

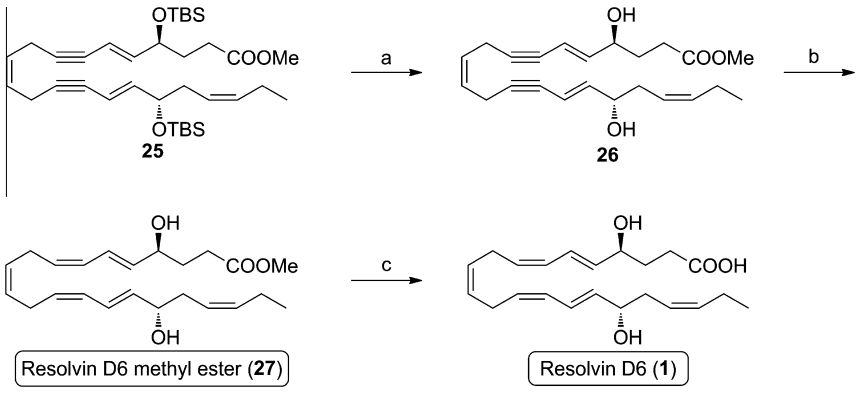
NMR indicated only minimal amount of *trans*-isomer present. Silver catalyzed monodesilylation of **22** with 2 equiv of $AgNO_3$ in CH_3OH/H_2O at 0 °C followed by treatment with NaCN and extractive work-up with hexane/ethyl acetate gave **4**.[33,34] It should be noted that 1 equiv of $AgNO_3$ was not sufficient and produced a mixture of starting material and **4** in a ratio of 1:1.

The skeleton of RvD6 was obtained from the key intermediates **2**, **3**, and **4** as outlined in Scheme 4. Pd^0/Cu^I coupling of **3** with **4** produced compound **23**.[35] Desilylation using $AgNO_3$ followed by NaCN work-up gave **24**, that was used without further purification in the second Sonogashira coupling with **2** to give the diacetylene precursor of RvD6 methyl ester (**25**).

The synthesis was completed as outlined in Scheme 5 via deprotection of the TBS groups of compound **25** with catalytic HCl, generated in situ from acetyl chloride in absolute methanol at 0 °C, to give **26**. Zn(Cu/Ag) reduction of **26** in CH_3OH/H_2O at 50 °C (24 h)



Scheme 4. *Reagents and conditions:* (a) $Pd(PPh_3)_4$, CuI, *n*-$PrNH_2$, benzene, rt; (b) $AgNO_3$, CH_3OH, H_2O, NaCN, 0 °C.



Scheme 5. *Reagents and conditions:* (a) MeCOCl, CH_3OH, 0 °C to rt; (b) Zn(Cu/Ag), CH_3OH, H_2O, 50 °C; and (c) 1 N LiOH, H_2O, THF, 0 °C, then H^+ (NaH_2PO_4 saturated).

gave RvD6 methyl ester (**27**).[36,37] Mild alkaline hydrolysis of **27** with LiOH in H_2O/THF at 0 °C followed by acidification with sat. NaH_2PO_4 in the presence of ethyl acetate gave RvD6 (**1**).

In summary, a concise total synthesis of RvD6 has been achieved,[38] making this anti-inflammatory lipid mediator from docosahexaenoic acid available for further biological testing. The synthesis of other Resolvins, Maresin, and Neuroprotectin D1 will be reported in due course.

Acknowledgments

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38. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **8**: ^1H NMR ($CDCl_3$, 300 MHz): δ 4.4 (t, J = 6.2 Hz, 1H),

3.7 (s, 3H), 2.6–2.4 (m, 2H), 2.3 (br s, 1H), 2.1–1.9 (m, 2H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.95, 105.73, 90.05, 61.86, 51.68, 32.41, 29.71, −0.20 (3C). Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.5–4.4 (dt, J = 6.0, 2.1 Hz, 1H), 3.7 (s, 3H), 2.7–2.4 (m, 2H), 2.5–2.4 (d, J = 2.1 Hz, 1H), 2.1–2.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.86, 84.06, 73.37, 61.36, 51.68, 32.40, 29.65. Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.4 (dt, J = 6.0, 1.8 Hz, 1H), 3.6 (s, 3H), 2.5–2.4 (t, J = 7.6, 2H), 2.4 (d, J = 1.8 Hz, 1H), 2.1–1.9 (m, 2H), 0.9 (s, 9H), 0.1 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.61, 84.67, 72.58, 61.61, 51.48, 33.41, 29.40, 25.71 (3C), 18.14, −4.69, −5.18. Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.1–6.0 (d, J = 19.2 Hz, 1H), 6.0–5.8 (dd, J = 19.2, 5.7 Hz, 1H), 4.1 (m, 1H), 3.6 (s, 3H), 2.4–2.3 (br t, J = 7.5 Hz, 2H), 1.9–1.7 (m, 2H), 1.5–1.4 (quint, J = 7.5 Hz, 6H), 1.4–1.2 (hex, J = 7.5 Hz, 6H), 0.9 (s, 9H), 1.0–0.8 (m, 15H), 0.01 (s, 3H), 0.005 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.16, 150.96, 127.87, 75.44, 51.30, 32.91, 29.74, 29.14 (3C), 27.21 (3C), 25.93 (3C), 18.27, 13.58 (3C), 9.60 (3C), −4.31, −4.83. Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.5–6.4 (dd, J = 14.4, 5.7 Hz, 1H), 6.2 (dd, J = 14.4, 1.5 Hz, 1H), 4.2–4.1 (m, 1H), 3.6 (s, 3H), 2.4–2.3 (t, J = 7.5 Hz, 2H), 1.9–1.7 (m, 2H), 0.9 (s, 9H), 0.01 (s, 3H), 0.001 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.77, 148.32, 76.41, 73.85, 51.55, 32.13, 29.02, 25.78 (3C), 18.15, −4.61, −5.02. Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.0–5.8 (dtt, J = 15.0, 5.7, 1.8 Hz, 1H), 5.7–5.6 (dtt, J = 15.0, 5.4, 1.5 Hz, 1H), 4.1 (m, 2H), 2.9 (m, 2H), 2.2–2.1 (qt, J = 7.5, 2.4 Hz, 2H), 1.1 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 130.28, 127.32, 84.07, 76.01, 63.13, 21.68, 14.15, 12.37. Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.9 (dd, J = 12.6, 2.1 Hz, 1H), 3.6 (dd, J = 12.6, 4.2 Hz, 1H), 3.1 (m, 2H), 2.6–2.5 (ddt, J = 17.4, 4.2, 2.4 Hz, 1H), 2.5–2.4 (ddt, J = 17.4, 4.8, 2.4 Hz, 1H), 2.2–2.1 (qt, J = 7.5, 2.4 Hz, 2H), 2.1(br s, 1H), 1.1 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 84.18, 73.27, 61.26, 57.83, 53.61, 21.67, 13.96, 12.31. Compound **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 5.4–5.2 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 3.9 (dd, J = 12.6, 2.4 Hz, 1H), 3.6 (dd, J = 12.6, 4.2 Hz, 1H), 3.0–2.9 (m, 2H), 2.5–2.2 (m, 2H), 2.1–1.9 (m, 2H), 1.9–1.8 (br s, 1H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 134.92, 122.36, 61.75, 57.95, 55.29, 29.23, 20.66, 14.06. Compound **3**: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 6.5 (dd, J = 14.4, 5.7 Hz, 1H), 6.2 (d, J = 14.4 Hz, 1H), 5.5 (m, 1H), 5.3 (m, 1H), 4.1 (br q, J = 6.0 Hz, 1H), 2.2 (m, 2H), 2.0 (br quint, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 148.80, 134.24, 123.62, 75.66, 75.08, 35.57, 25.81 (3C), 20.73, 18.21, 14.18, −4.63, −4.83. Compound **20**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.0–5.8 (m, 2H), 4.1–3.9 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 129.31 (2C), 24.26 (2C). Compound **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (m, 2H), 3.0–2.9 (m, 4H), 0.1 (s, 18H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 126.08 (2C), 104.32 (2C), 84.85 (2C), 18.44 (2C), 0.06 (6C). Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (m, 2H), 3.0–2.9 (m, 4H), 2.0 (t, J = 2.7 Hz, 1H), 0.1 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 126.25, 125.76, 104.08, 84.90, 81.90, 68.42, 18.37, 16.91, 0.03 (3C). Compound **23**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.1–6.0 (dd, J = 15.9, 5.1 Hz, 1H), 5.7–5.5 (m, 3H), 5.5–5.2 (m, 2H), 4.2–4.0 (m, 1H), 3.1–2.9 (m, 4H), 2.3–2.1 (m, 2H), 2.1–1.9 (br quint, J = 7.5 Hz,, 2H), 0.93 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.13 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.15, 133.85, 126.34, 125.87, 124.23, 109.11, 104.36, 87.56, 84.85, 78.99, 72.69, 36.03, 25.89 (3C), 20.75, 18.40, 18.23, 17.96, 14.09, 0.06 (3C), −4.52, −4.76. Compound **26**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.1–5.9 (2dd, J = 15.7, 6.0 Hz, 2H), 5.8–5.5 (m, 5H), 5.4–5.2 (m, 1H), 4.2–4.1 (m, 2H), 3.6 (s, 3H), 3.1–3.0 (m, 4H), 2.4 (m, 2H), 2.3 (br t, J = 6.9 Hz, 2H), 2.1–2.0 (br quint, J = 7.5 Hz, 2H), 2.0–1.7 (m, 2H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.24, 144.05, 143.79, 135.65, 126.15, 125.97, 123.24, 110.80, 110.32, 88.52, 88.16, 78.63, 78.47, 71.63, 71.30, 51.70, 34.96, 31.60, 29.87, 20.72, 17.85, 17.82, 14.11. Compound **27**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.7–6.5 (m, 2H), 6.1–5.9 (br t, J = 11.1 Hz 2H), 5.8–5.7 (dd, J = 15.3, 6.0 Hz, 1H), 5.7–5.6 (dd, J = 15.3, 6.3 Hz, 1H), 5.6–5.3 (m, 6H), 4.2–4.1 (m, 2H), 3.6 (s, 3H), 3.1–2.9 (m, 4H), 2.4 (dt, J = 7.5, 1.2 Hz, 2H), 2.3–2.2 (br t, J = 6.9 Hz, 2H), 2.1 (quint, J = 7.5 Hz, 2H), 1.9–1.7 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.22, 137.56, 137.21, 133.94, 130.04, 129.80, 128.66, 128.56, 128.40, 128.35, 125.31, 125.13, 124.98, 71.87, 71.08, 51.36, 35.59, 32.64, 30.13, 26.24 (2C), 20.81, 13.88. Compound **1**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.7–6.5 (br dd, J = 15.3, 11.1 Hz, 2H), 6.1–6.0 (br t, J = 11.1 Hz, 2H), 5.8–5.6 (m, 2H), 5.6–5.3 (m, 6H), 4.2–4.1 (q, J = 6.3 Hz, 2H), 3.1–2.9 (m, 4H), 2.4 (t, J = 7.5, 1.2 Hz, 2H), 2.3–2.2 (br t, J = 6.9 Hz, 2H), 2.3–2.1 (br s, 2H), 2.1 (quint, J = 7.5 Hz, 2H), 1.9–1.7 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.85, 137.79, 137.48, 134.26, 130.36, 130.13, 128.95, 128.86, 128.69 (2C), 125.65, 125.41, 125.33, 72.19, 71.46, 35.89, 32.82, 30.26, 26.55 (2C), 21.11, 14.18. UV (EtOH) λ_{max} 232 nm. HPLC/API-ES/MS (m/z): 383.5 $[M+Na^+]^+$.

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Corresponding Author's Institution: University of Medicine and Dentistry of New Jersey

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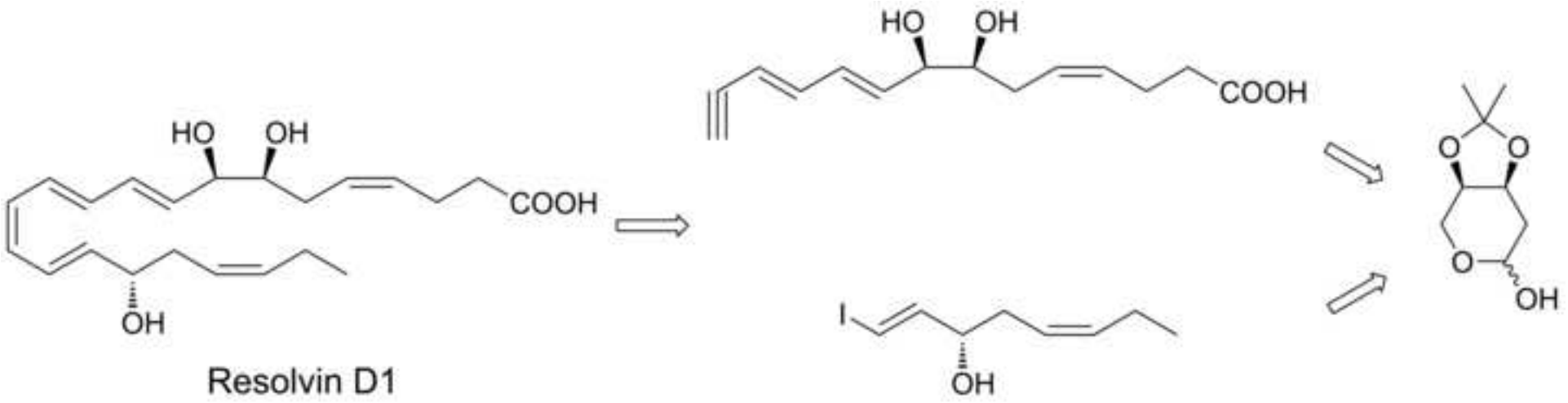
*Graphical Abstract (for review)



Prof. Dr. Bernd W. Spur October 9, 2012

Professor Dr. John Wood
Department of Chemistry
Colorado State University
Fort Collins, CO 80523-1872

Dear Professor Wood,

We thank the reviewer for his comments. The manuscript has been revised accordingly to the reviewer's comments:

- In Scheme 2 reagents and conditions "c and d" have been replaced by "b and c"

Sincerely yours,

Bernd W. Spur Ph.D.

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Total synthesis of Resolvin D1, a potent anti-inflammatory lipid mediator

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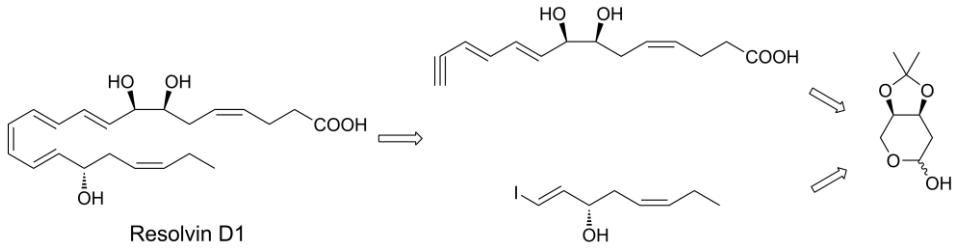

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Total synthesis of Resolvin D1, a potent anti-inflammatory lipid mediator

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ABSTRACT

The total synthesis of Resolvin D1, a potent endogenous anti-inflammatory lipid mediator derived from docosahexaenoic acid, has been achieved. The chiral hydroxy-groups at C7, C8 and C17 were obtained via a chiral pool strategy from 2-deoxy-D-ribose. Wittig reactions followed by a modified Pd^0/Cu^I Sonogashira coupling and Zn(Cu/Ag) *cis*-reduction completed the total synthesis of Resolvin D1.

The health benefits of the ω-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid in a variety of human diseases such as asthma, rheumatoid arthritis and cardiovascular diseases are well documented in the literature.[1-3] The effects of these ω-3 fatty acids on neutrophil function were explored in healthy volunteers in order to establish a biochemical mechanism of the observed effects in humans.[4] In 2002 Serhan and collaborators could show for the first time that the enzymatic conversion of these polyunsaturated fatty acids by different lipoxygenase enzymes led to a series of highly potent anti-inflammatory lipid mediators named Resolvins (resolution phase interaction products).[5] Later on they discovered the Neuroprotectins and Maresin 1 (macrophage mediator in resolving inflammation).[6,7] These novel pro-resolving lipids are generated at the side of injury and they participate actively in the resolution of inflammation. It has been reported that Resolvin D1 attenuates inflammatory pain under a variety of conditions including arthritic pain.[8,9] In addition Resolvin D1 promotes the resolution of allergic airways responses.[10] Recently Chiang, Serhan and collaborators reported that bacterial infections contribute to the active resolution of acute inflammation.[11] They identified Resolvin D1 (RvD1) among others in self-resolving *Escherichia coli* exudates. In human macrophages RvD1 promotes phagocytosis of *E. coli* and as a result Resolvin D1 accelerated the resolution to enhance survival towards gram-positive and gram-negative bacteria and lowered the requirement of concurrent antibiotic treatment.[11] These findings offer a potential new strategy to overcome the problems associated with antibiotic resistance towards bacteria.

((Figure 1))

The biosynthesis of Resolvin D1 is shown in Figure 1. Resolvin D1 is formed in vivo from docosahexaenoic acid via lipoxygenation at C17 and C7. Elimination of H_2O forms the 7*S*,8*S*-epoxide intermediate that undergoes enzymatic epoxide opening to produce the 7*S*,8*R*,17*S*-trihydroxy-docosahexaenoic acid (Resolvin D1).[12,13]

In order to explore the full potential of these Resolvins they have to be prepared by total syntheses since the availability from natural sources is limited to microgram quantities.[14-27]

As part of our studies on the total syntheses of lipid mediators of resolution we wish to report a convergent total synthesis of Resolvin D1 [RvD1; (4*Z*,7*S*,8*R*,9*E*,11*E*,13*Z*,15*E*,17*S*,19*Z*)-7,8,17-trihydroxy-4,9,11,13,15,19-docosahexaenoic acid (**1**)]. As shown in the retrosynthetic scheme (Figure 2) 3,4-*O*-isopropylidene-2-deoxy-D-ribose was used as the source of chirality for C7, C8 and C17. Wittig reactions and Sonogashira coupling followed by *cis*-selective Zn(Cu/Ag) reduction produced Resolvin D1 (**1**).

((Figure 2))

The synthesis of the C1-C14 key intermediate **3** was achieved in 5 steps starting from the readily available 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**2**)[28] (Scheme 1). *Cis*-selective Wittig reaction of **2** with 2.2 equiv of the phosphorane generated from (Methoxycarbonylpropyl)triphenylphosphonium bromide (**6**) and $KN(TMS)_2$ in THF gave the isopropylidene ester **9**. Dess Martin oxidation of **9** in CH_2Cl_2 produced the aldehyde **10** in 84% yield.[29] The use of PCC in the presence of sodium acetate gave slightly lower yields.[30] The aldehyde **10** was converted to

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11 in 2-steps. Wittig reaction of **10** with the phosphorane generated from the corresponding phosphonium bromide **7**[31] and *n*-BuLi in THF followed by catalytic iodine isomerization in benzene at rt gave the *trans*,*trans*-diene **11** in high yield. A small amount of the remaining 9-*cis*-isomer could be easily removed by flash chromatography. Cleavage of the terminal TMS-group with potassium fluoride dihydrate in DMF in the presence of a catalytic amount of 18-crown-6 gave the key intermediate **3** in 88% yield.[32]

((Scheme 1))

The C15-C22 fragment **4** was obtained in 3 steps from 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**2**) as outlined in Scheme 2. Wittig reaction of **2** with 2.5 equiv of the phosphorane generated from the phosphonium bromide **8** and $NaN(TMS)_2$ in ether at –78 ºC gave the *cis*-olefination product **5**.[14] Using the method of Samuelsson **5** was converted into the iodide **12** with triphenylphosphine, imidazole and iodine in toluene at 60 ºC in 82% yield.[33-35] The isopropylidene iodide **12** was converted to the *trans*-iodovinyl alcohol **4** using 4 equiv of LDA in THF at –78 ºC. This reaction also produced the propargyl alcohol **13** that was separated by flash chromatography. The *cis*-iodovinyl alcohol isomer of **4** was not observed. This new strategy is the shortest approach to alcohol **4**, previously used in our syntheses of Resolvin D5[15] and Resolvin D6.[22]

((Scheme 2))

The total synthesis of Resolvin D1 was completed as shown in Scheme 3. Modified Sonogashira coupling[36,37] of **4** in the presence of $Pd(PPh_3)_4$,[38] CuI, and piperidine in benzene with very slow addition of the acetylene **3** gave the isopropylidene protected acetylene precursor of Resolvin D1 methyl ester (**14**) in 86% yield.[39] Under these conditions no dimerization of acetylene **3** was detected. Mild cleavage of the isopropylidene protective group with a catalytic amount of acetyl chloride in CH_3OH at 0 ºC gave **15**. The *cis*-selective reduction of the conjugated triple bond was achieved with freshly prepared Zn(Cu/Ag)[40] in CH_3OH/H_2O at 50 ºC to produce Resolvin D1 methyl ester (**16**) in 67% yield after HPLC purification.[41,42] Mild hydrolysis of the methyl ester **16** with 1 N LiOH in CH_3OH/H_2O at 0 ºC under argon gave after acidification with sat. NaH_2PO_4 in the presence of ethyl acetate Resolvin D1 (**1**) in 94% yield. HPLC analysis showed that the synthetic **1** co-eluted with an authentic sample of Resolvin D1 (Cayman Chemical Company).[43]

((Scheme 3))

In summary, a short and concise total synthesis of Resolvin D1 from 3,4-*O*-isopropylidene-2-deoxy-D-ribose has been achieved,[43] making this important lipid mediator of resolution available for further biological and pharmacological testing. The synthesis of other Resolvins and Neuroprotectin D1 will be reported in due course.

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38. Tetrakis(triphenylphosphine)palladium(0) 99% (99.9%-Pd) from Strem Chemicals, catalog # 46-2150, was used.
39. In a flame dried flask under argon CuI (5.2 mg, 0.027 mmol) and tetrakis(triphenylphosphine)palladium(0) (15.8 mg, 0.014 mmol) were added followed by a solution of **4** (69 mg, 0.27 mmol) in benzene (2 ml). The solution was alternatively evacuated and flushed with argon and then piperidine (54 µl, 0.55 mmol) was added. The flask was protected from light and a solution of **3** (75 mg, 0.25 mmol) in benzene (2.2 ml), previously saturated with argon, was added over a period of 2 hours with a syringe pump. The reaction mixture was stirred for 2 additional hours and then quenched by the addition of a saturated solution of NH_4Cl. The resulting suspension was extracted with ether and the organic layer was washed with NH_4Cl, NaCl and dried over Na_2SO_4. Concentration followed by flash chromatography purification (silica gel, hexane:EtOAc 85:15 → 80:20) afforded 92 mg (86%) of **14**.
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41. HPLC [Zorbax SB-C18, 21.2 mm x 25 cm, 325 nm, CH_3OH/H_2O 63/37, 10 mL/min, tR(RvD1-Me) = 65 min].
42. When the reaction was performed in CD_3OD/D_2O the 13,14-dideuterio-Resolvin D1 methyl ester was cleanly produced.
43. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5–5.4 (m, 2H), 4.2–4.1 (m, 2H), 3.7–3.6 (m, 2H), 3.6 (s, 3H), 2.5–2.2 (m, 6H), 1.8 (br s, 1H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.45, 130.14, 126.37, 108.21, 77.78, 76.66, 61.69, 51.52, 33.78, 28.06, 27.45, 25.37, 23.01. Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.7–9.6 (dd, *J* = 3.0, 0.6 Hz, 1H), 5.6–5.4 (m, 2H), 4.4–4.3 (m, 1H), 4.3 (dd, *J* = 7.2, 3.0 Hz, 1H), 3.6 (s, 3H), 2.4–2.2 (m, 6H), 1.6 (s, 3H), 1.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 201.65, 173.34, 130.88, 125.32, 110.61, 81.91, 78.23, 51.51, 33.63, 27.86, 27.43, 25.19, 22.98. Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.7–6.5 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.4–6.2 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.8–5.7 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.7–5.6 (d, *J* = 15.6 Hz, 1H), 5.5–5.3 (m, 2H), 4.6–4.5 (m, 1H), 4.2–4.1 (dt, *J* = 8.4, 5.8 Hz, 1H), 3.6 (s, 3H), 2.4–2.0 (m, 6H), 1.5 (s, 3H), 1.3 (s, 3H), 0.2 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ C1 not observed, 141.54, 132.23, 131.85, 129.96, 126.36, 112.16, 108.50, 104.08, 97.86, 78.60, 78.30, 51.51, 33.85, 28.87, 28.10, 25.50, 23.04, -0.12 (3C). Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.7–6.6 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.4–6.2 (ddt, *J* = 15.0, 10.8, 0.9 Hz, 1H), 5.8–5.7 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.6 (br dd, *J* = 15.6, 2.4 Hz, 1H), 5.5–5.3 (m, 2H), 4.6–4.5 (m, 1H), 4.2–4.1 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.6 (s, 3H), 3.1–3.0 (d, *J* = 2.4 Hz, 1H), 2.4–2.1 (m, 6H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ C1 not observed, 142.28, 132.40, 131.88, 130.01, 126.48, 111.11, 108.59, 82.71, 79.88, 78.63, 78.45, 51.39, 33.94, 29.02, 28.12, 25.53, 23.16. Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 5.4–5.3 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 4.4–4.3 (m, 1H), 4.2–4.1 (td, *J* = 7.2, 5.7 Hz, 1H), 3.2–3.1 (m, 2H), 2.3 (br t, *J* = 7.2 Hz, 2H), 2.1–2.0 (br quint, *J* = 7.5 Hz, 2H), 1.5 (s, 3H), 1.3 (s, 3H), 1.0 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 134.44, 123.63, 108.52, 78.30, 77.69, 28.36, 27.45, 25.68, 20.86, 14.00, 3.66. Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.5 (dd, *J* = 14.4, 6.0 Hz, 1H), 6.4–6.3 (dd, *J* = 14.4, 1.5 Hz, 1H), 5.7–5.5 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 5.4–5.2 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 4.2–4.0 (m, 1H), 2.4–2.2 (m, 2H), 2.1–2.0 (quint d, *J* = 7.5, 1.5 Hz, 2H), 1.7–1.6 (br s, 1H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 147.90, 136.07, 122.74, 77.08, 73.91, 34.64, 20.75, 14.14. Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.5 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 5.5–5.3 (dtt, *J* = 10.8, 7.5, 1.5 Hz, 1H), 4.4–4.3 (m, 1H), 2.5–2.4 (m, 2H), 2.4 (d, *J* = 2.1 Hz, 1H), 2.1–2.0 (br quint, *J* = 7.5 Hz, 2H), 1.9 (d, *J* = 5.7 Hz, 1H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.13, 122.43, 84.56, 72.90, 61.88, 35.47, 20.79, 14.14. Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6–6.5 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.4–6.2 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.2–6.1 (dd, *J* = 15.9, 5.7 Hz, 1H), 5.9–5.7 (m, 3H), 5.6–5.5 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 5.5–5.4 (m, 2H), 5.4–5.2 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 4.6–4.5 (br t, *J* = 6.9 Hz, 1H), 4.2–4.1 (m, 2H), 3.6 (s, 3H), 2.4–2.0 (m, 10H), 1.5 (s, 3H), 1.3 (s, 3H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.40, 144.91, 140.36, 135.79, 132.45, 131.34, 129.92, 126.37, 123.10, 112.31, 110.04, 108.47, 90.73, 89.41, 78.66, 78.30, 71.56, 51.50, 34.97, 33.84, 28.87, 28.09, 25.49, 23.03, 20.72, 14.11. Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.7–6.5 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.4–6.3 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.2–6.1 (dd, *J* = 15.9, 5.7 Hz, 1H), 5.9–5.7 (m, 3H), 5.7–5.5 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 5.5–5.4 (m, 2H), 5.4–5.2 (dtt, *J* = 10.8, 7.2, 1.5 Hz, 1H), 4.3–4.1 (m, 2H), 3.8–3.6 (dt, *J* = 9.0, 3.9 Hz, 1H), 3.6 (s, 3H), 2.5–2.0 (m, 10H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.73, 144.87, 140.60, 135.83, 133.59, 131.81, 131.08, 126.67, 123.13, 112.13, 110.14, 90.64, 89.49, 74.75, 73.91, 71.63, 51.61, 35.03, 33.59, 30.12, 22.75, 20.75, 14.10. Compound **16**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.9–6.7 (m, 2H), 6.5–6.3 (m, 2H), 6.1–6.0 (m, 2H), 5.9–5.7 (m, 2H), 5.6–5.3 (m, 4H), 4.3–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.6–3.5 (m, 1H), 3.1 (d, *J* = 4.8 Hz, 1H), 3.0–2.9 (d, *J* = 4.5 Hz, 1H), 2.9–2.8 (d, *J* = 5.1 Hz, 1H), 2.4–2.0 (m, 10H), 1.0 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ C1 not observed, 138.77, 134.55, 134.17, 133.92, 132.19, 130.15, 129.84, 129.66, 128.45, 128.06, 125.41, 125.24, 75.32, 74.87, 72.04, 51.54, 35.70, 34.08, 30.98, 23.28, 20.98, 14.06. Compound **1**: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.8–6.6 (m, 2H), 6.5–6.2 (m, 2H), 6.1–5.9 (m, 2H), 5.9–5.8 (dd, *J* = 14.7, 6.7 Hz, 1H), 5.8–5.7 (dd, *J* = 15.0, 6.6 Hz, 1H), 5.6–5.3 (m, 4H), 4.2–4.1 (m, 1H), 4.1–3.9 (m, 1H), 3.6–3.5 (m, 1H), 2.4–2.1 (m, 8H), 2.1–2.0 (quint, *J* = 7.5 Hz, 2H), 1.0–0.9 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ C1 not observed, 138.29, 134.69, 134.57, 134.47, 133.44, 130.78, 130.46, 130.24, 129.19, 128.32, 126.61, 125.47, 76.27, 75.86, 73.13, 36.27, 34.95, 31.89, 24.06, 21.65, 14.46. UV (EtOH) λ_{max} 289, 302, 317 nm. HPLC-UV: Hypersil-ODS, 100x2.1 mm, 301 nm, CH_3OH/H_2O (0.1% formic acid) 45/55 to 70/30, 0.2 mL/min, tR = 21.4 min [synthesized **1** co-eluted with an authentic sample of Resolvin D1 (Cayman Chemical Company)]. HPLC/MS/MS (m/z): 375.3 $[M-H]^-$.

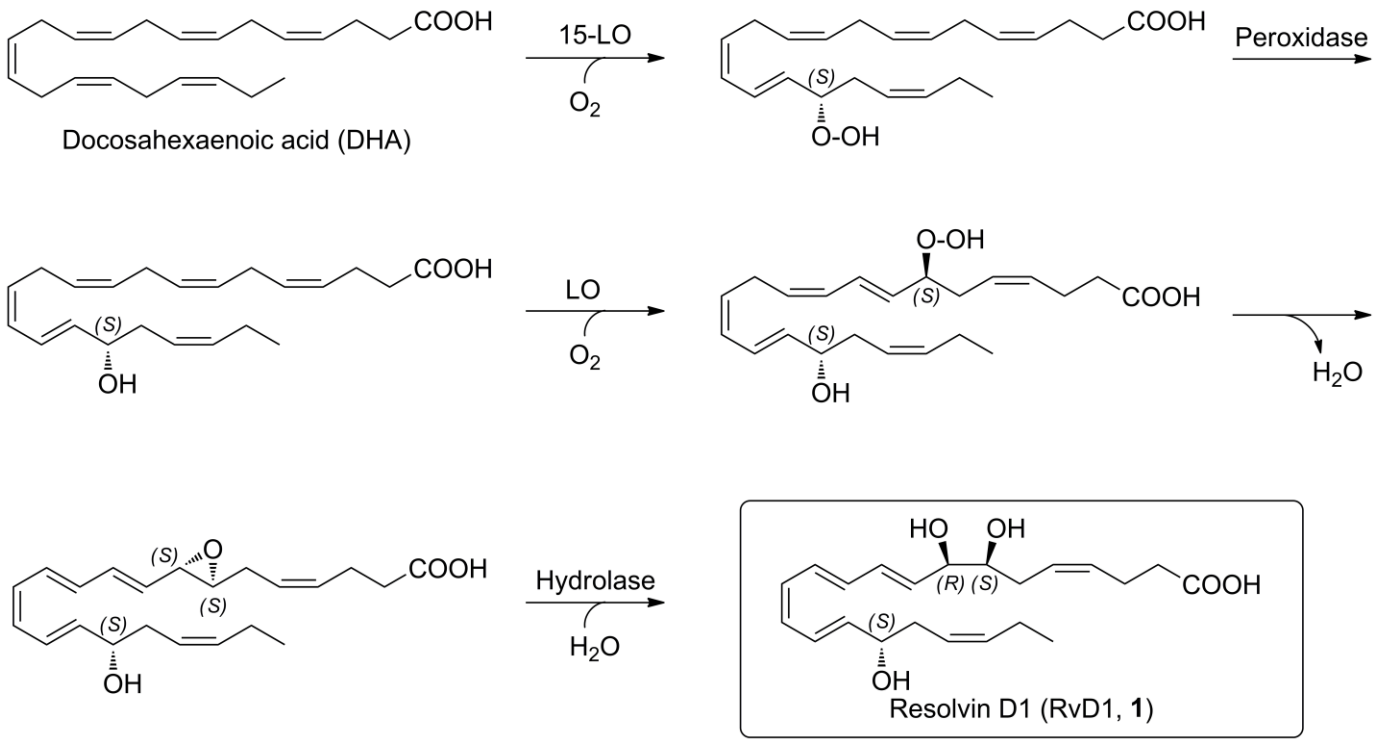


Figure 1. Biosynthesis of Resolvin D1.

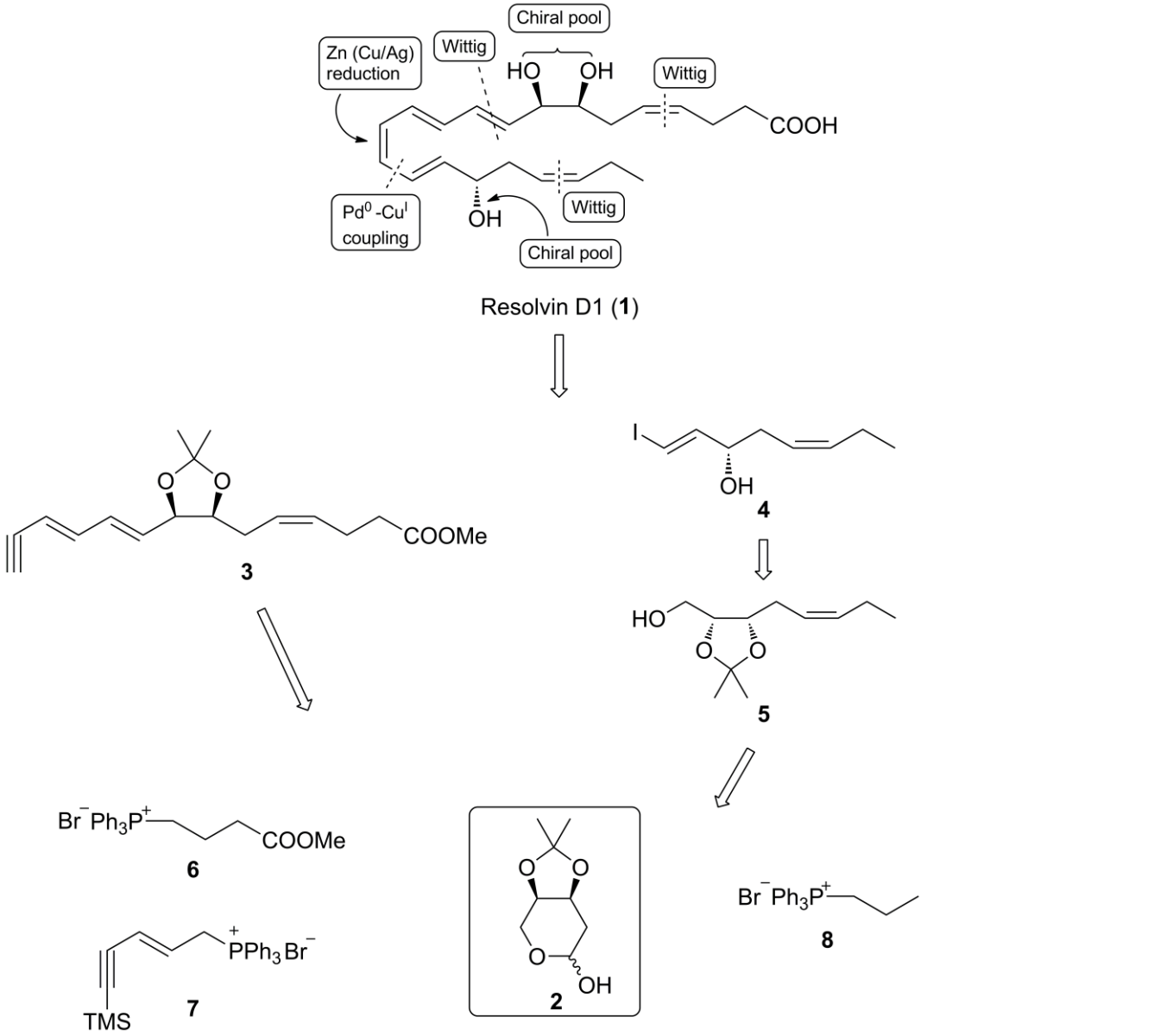
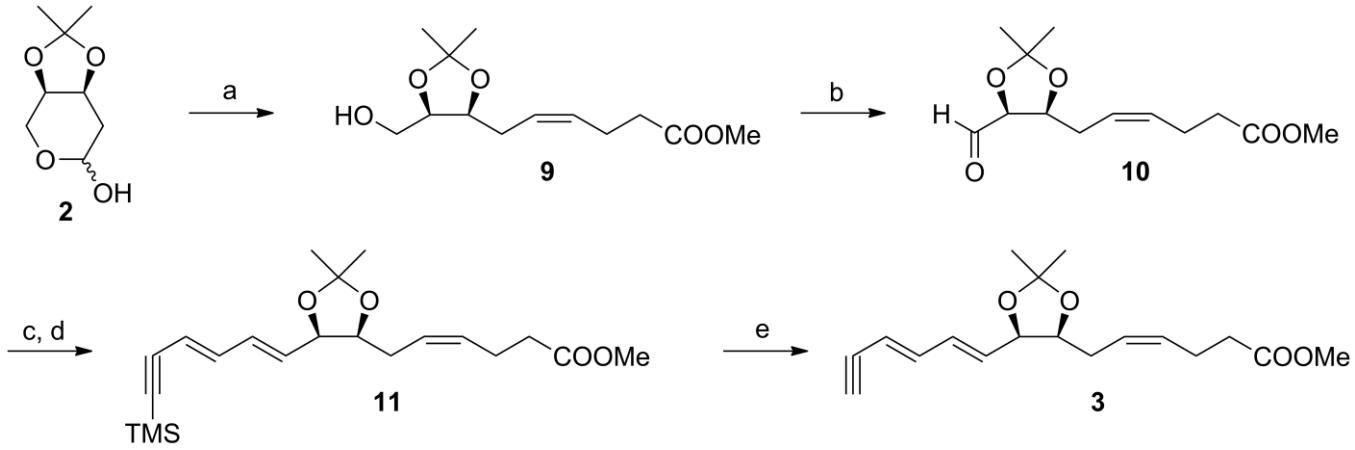
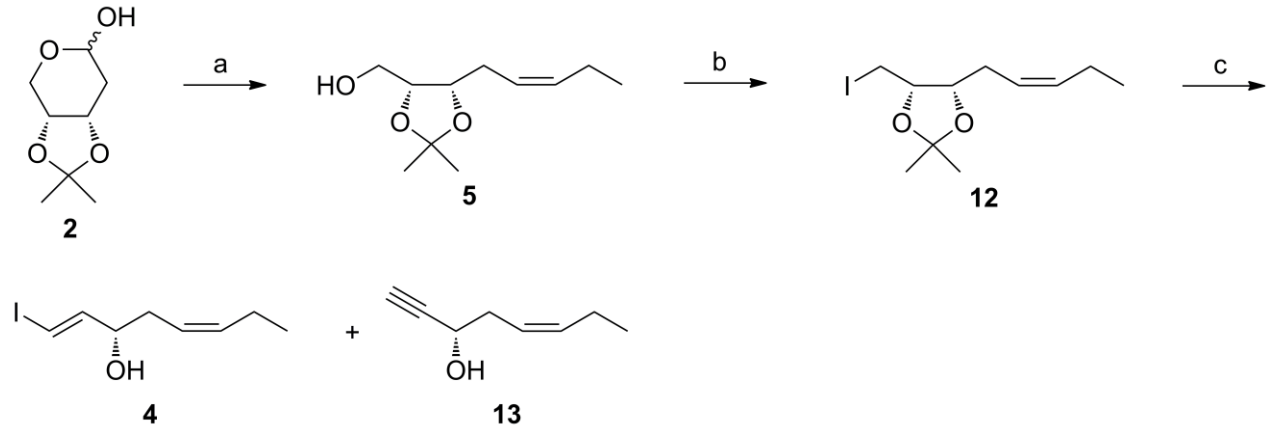


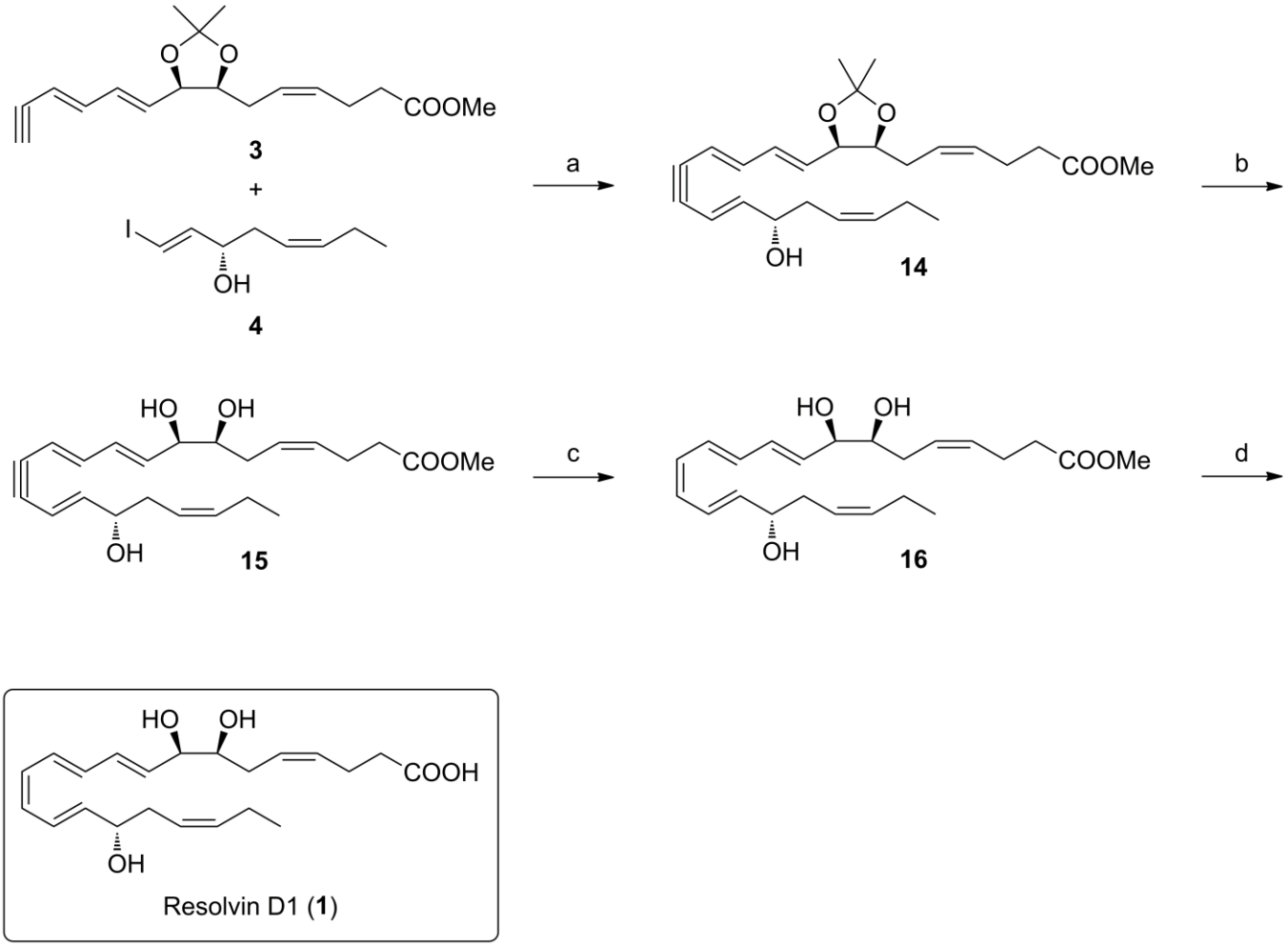
Figure 2. Retrosynthetic approach to Resolvin D1.



Scheme 1. *Reagents and conditions:* (a) **6**, $KN(TMS)_2$, THF, –70 °C to rt, 43%; (b) Dess-Martin periodinane, CH_2Cl_2, rt, 84%; (c) **7**, *n*-BuLi, THF, –78 ºC to 0 ºC, 80%; (d) I_2, benzene, rt, 87%; (e) $KF{\cdot}2H_2O$, 18-crown-6, DMF, rt, 88%.



Scheme 2. *Reagents and conditions:* (a) **8**, $NaN(TMS)_2$, Et_2O, –78 °C to rt, 60%; (b) I_2, Ph_3P, imidazole, toluene, 60 °C, 82%; (c) LDA, THF, –78 °C, 40% (**4**).



Scheme 3. *Reagents and conditions:* (a) $Pd(PPh_3)_4$, CuI, piperidine, benzene, rt, 86%; (b) CH_3COCl cat, CH_3OH, 0 °C, 90%; (c) Zn(Cu/Ag), CH_3OH, H_2O, 50 ºC, 5 h, 67%; (d) 1 N LiOH, CH_3OH, H_2O, 0 °C, then sat. NaH_2PO_4, 94%.

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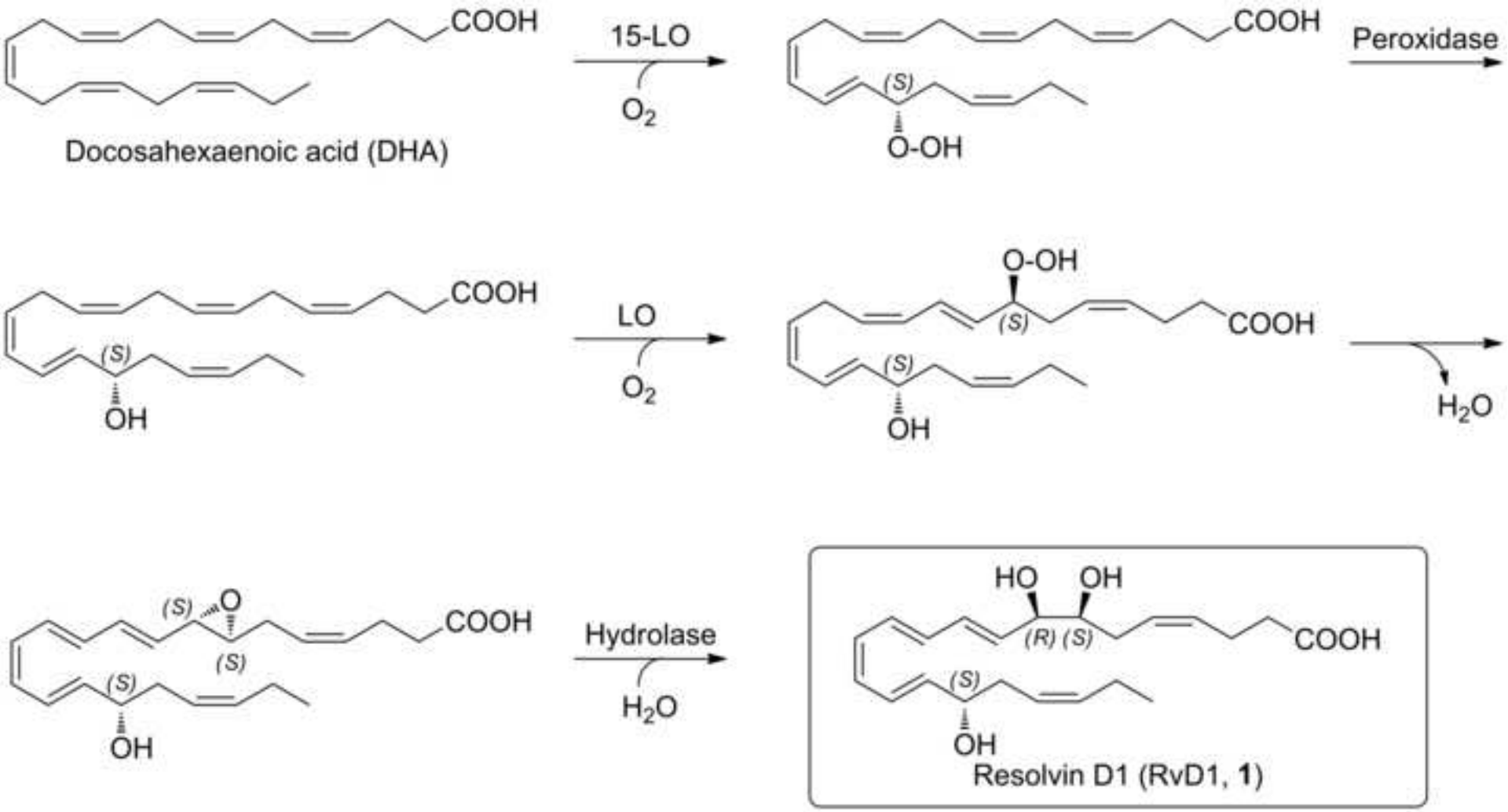

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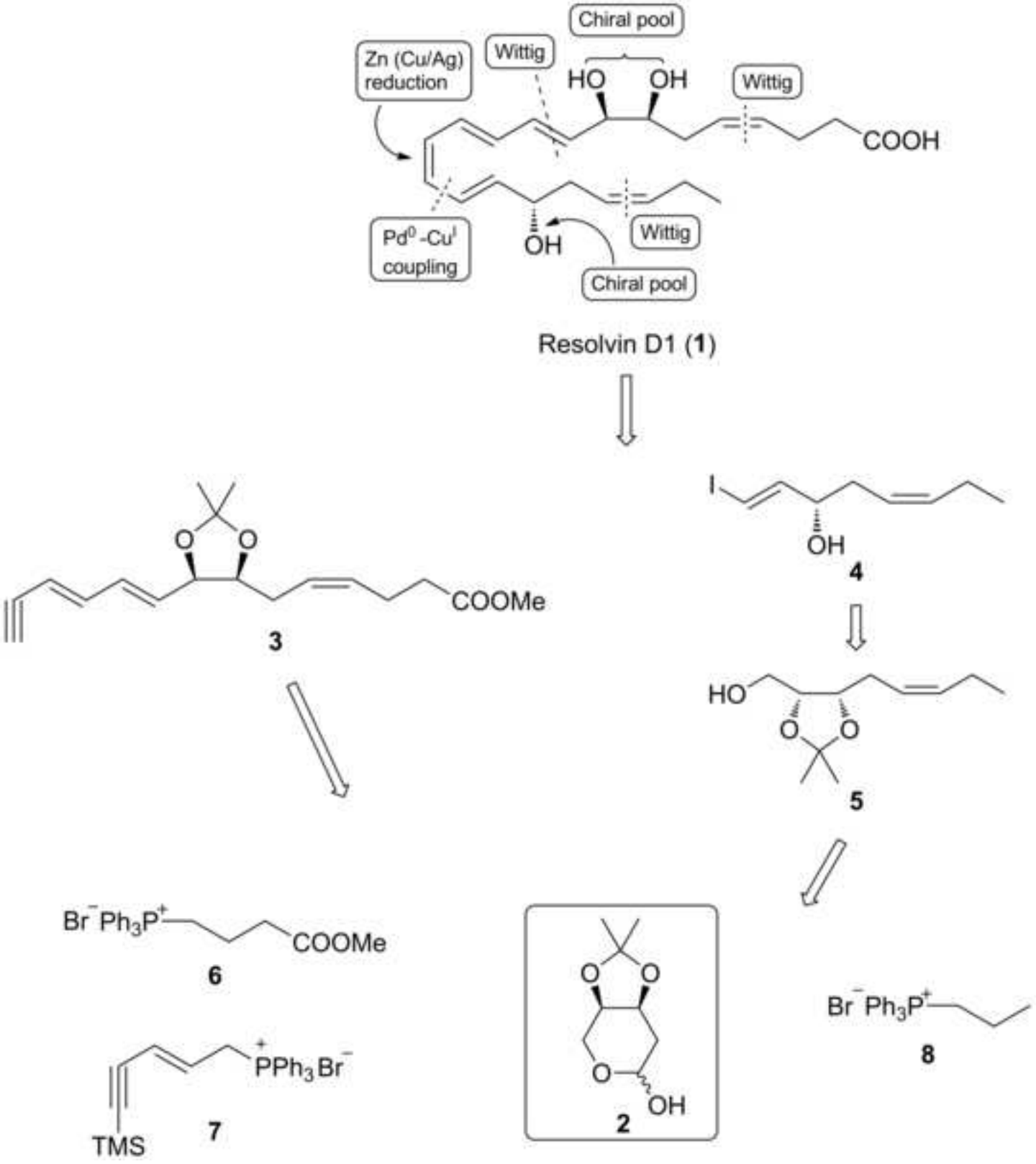

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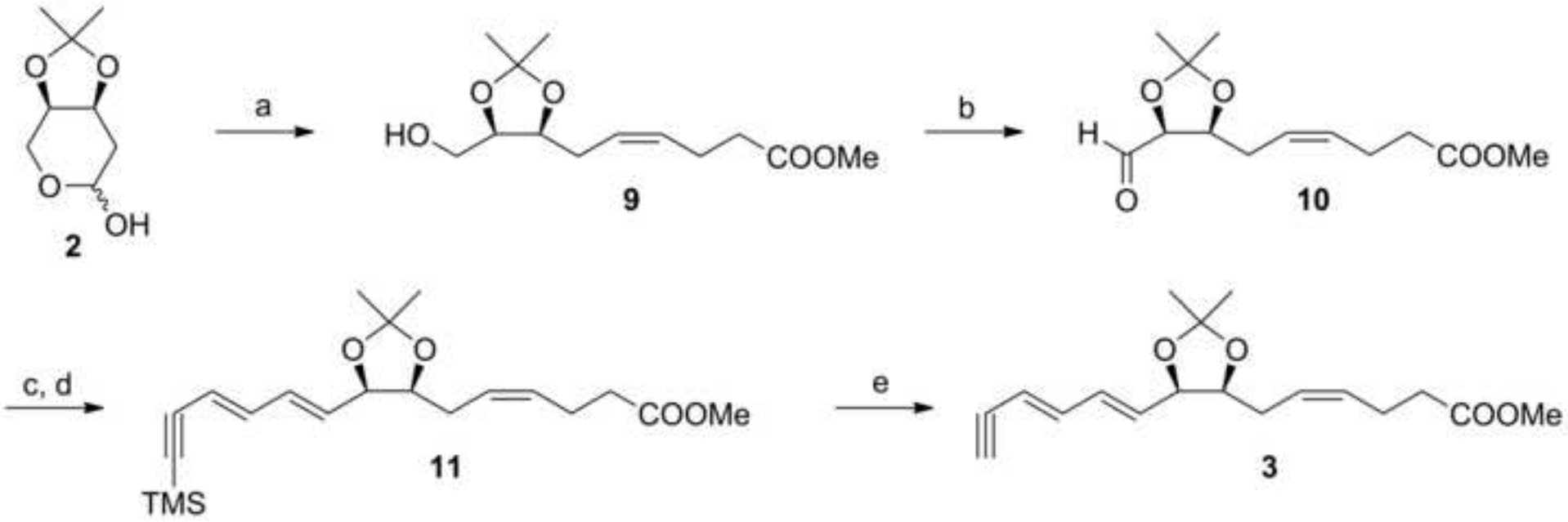

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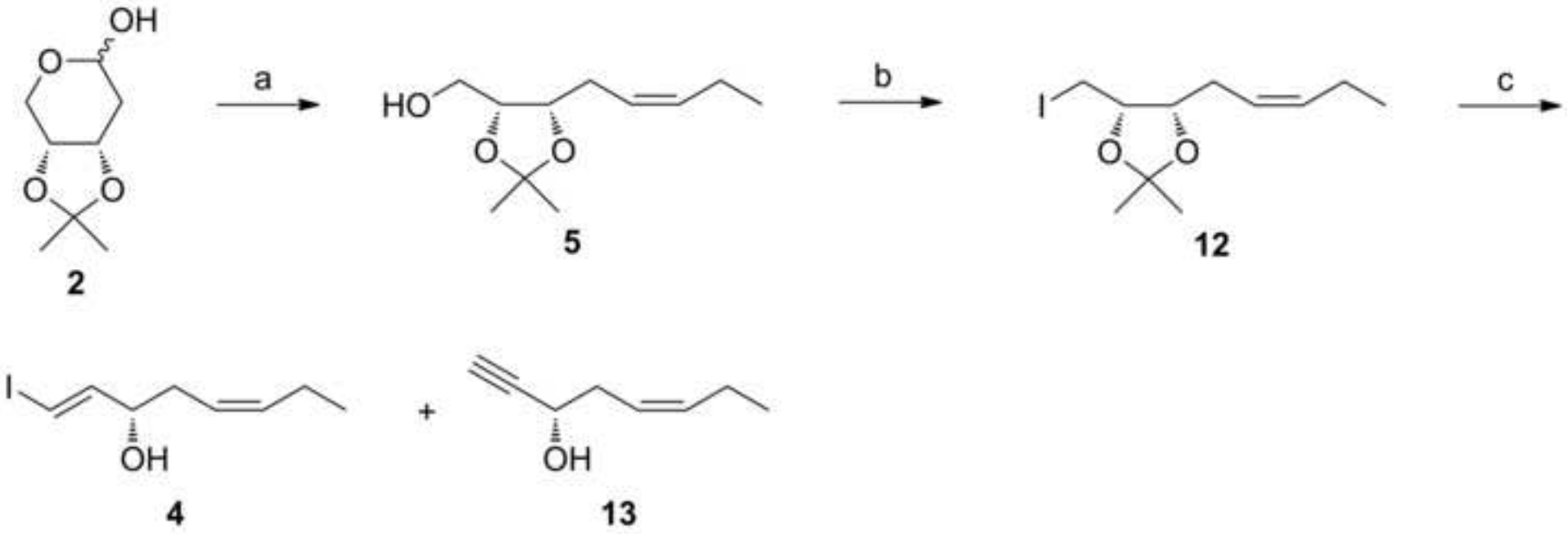

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